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A New Synthetic Route to Polyalkoxypyrimidines Based on the Reaction of Esters and Methyl Thiocyanate

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The reaction of aliphatic esters with methyl thiocyanate and triflic anhydride affords substituted 4-alkoxy-2,6-bis(methylthio)pyrimidines with minor amounts of substituted *S*-methyl *N*-alkanoylthiocarbamates. The structure of the starting ester appears to determine the ratio of final products. Methylthio groups on the pyrimidine ring can be easily converted into methylsulfonyl groups by oxidation. Controlled substitution of one or both methylsulfonyl groups leads to the formation of aminodialkoxy- and trialkoxypyrimidines.

Introduction

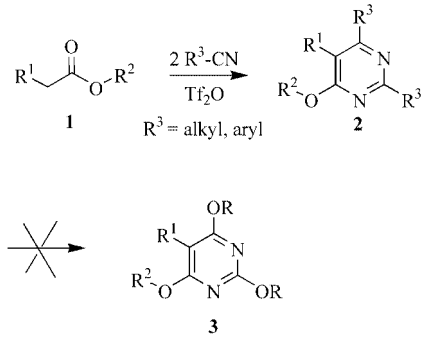
Alkoxypyrimidines derivatives are an important class of heterocyclic compounds with applications in several different areas. Thus, 4-alkoxypyrimidines are used as the basis for the design of compounds as potential inhibitors cyclin-dependent kinases 1 and 2,[1] while dimethoxypyrimidines are important intermediates for the preparation of antihypertensive and antithrombotic drugs.[2] Dimethoxypyrimidines are also employed as herbicides agents to control plant growth[3,4] or fungicides.[5] Trialkoxypyrimidine derivatives are versatile building blocks for the agrochemical industry. In particular, dialkoxypyrimidinyloxy salicylic acids derivatives represent a new class of substances exhibiting potent herbicide activity.[6,7]

The synthesis of polyalkoxypyrimidines derivatives often involves tedious multi-step procedures using expensive or toxic reagents and affording low yields.[8,9] Alternative methods generally employ the displacement of chlorine atoms from chloroazines derivatives.[1,10–12] Recently, 2,4-dimethoxypyrimidine derivatives have been prepared from uracils by Wittig olefination.[13]

In spite of their importance, there is no synthetic method to prepare polyalkoxypyrimidines from readily available starting materials with high yields in a few reaction steps. We describe herein the facile synthesis of a variety of substituted mono-, di- and trialkoxypyrimidines.

Results and Discussion

The cocyclization of nitriles and ketones in the presence of triflic anhydride was reported as an useful method to prepare alkyl- and arylpyrimidines.[14] The extension of this synthetic procedure to other carbonylic compounds leads to variously substituted pyrimidines and other nitrogen-containing rings.[15–21] The application of this methodology to the reaction of aliphatic esters **1** with nitriles affords the substituted 4-alkoxypyrimidines **2** in good yields (Scheme 1).[18] Access to the polyalkoxypyrimidines **3** via 4-alkoxypyrimidines involves several steps, some requiring harsh conditions. The importance of the di- and trialkoxypyrimidines prompted us to explore a different path to these target compounds.



Scheme 1.

The reaction of the aliphatic esters **1** with two equiv. of methyl thiocyanate in the presence of triflic anhydride

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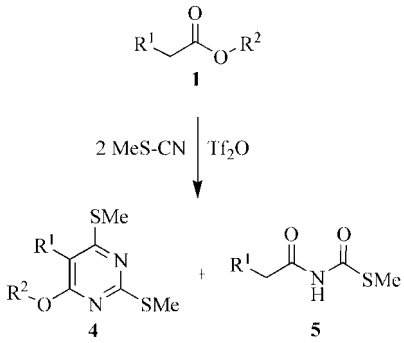
(Tf_2O) forms mainly 4-alkoxy-2,6-bis(methylthio)pyrimidines (**4**) with variable amounts of *S*-methyl alkanoylthiocarbamates (**5**) (Scheme 2 and Table 1). When alkyl acetates were used, *S*-methyl *N*-acetylthiocarbamate (**5a**) was the exclusive product.



Scheme 2.

Table 1. 4-Alkoxy-2,6-bis(methylthio)pyrimidines **4** and *S*-methyl *N*-alkanoylthiocarbamates **5**.

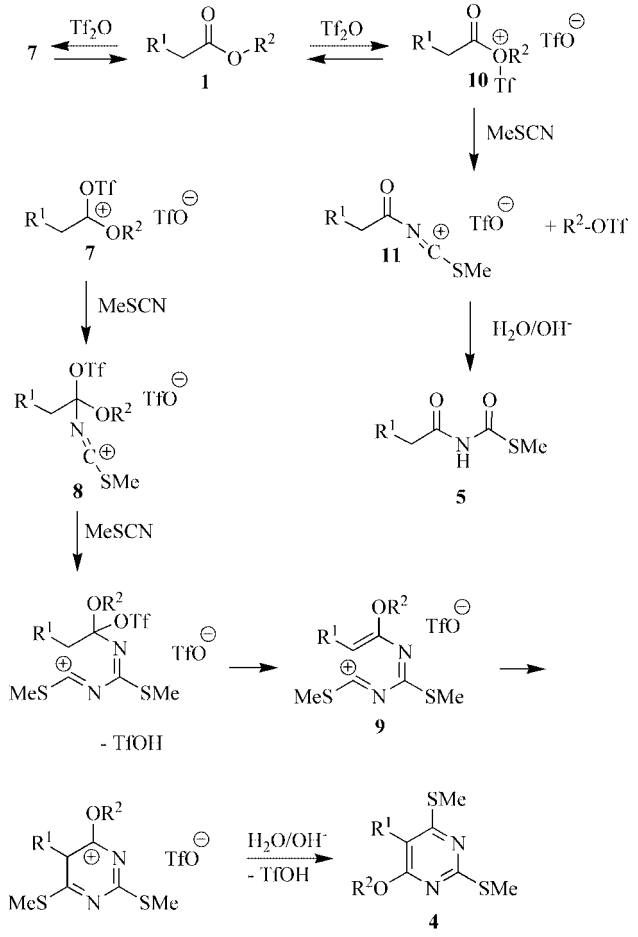
R^1	R^2	Yield[a]	Yield[a]
H	Et		**5a** (58%)
H	Pr		**5a** (51%)
Me	Et	**4b** (78%)	
Bu	Et	**4c** (42%)	**5c** (43%)
$CH_3(CH_2)_7$	Et	**4d** (45%)	**5d** (42%)
Ph	Et	**4e** (71%)	**6** (19%)
Me	Pr	**4f** (69%)	

[a] Isolated product.

Formation of the pyrimidines and carbamates can be explained with a mechanism outlined in Scheme 3. Electrophilic attack by Tf_2O at one of the two oxygen atoms of the ester group leads to the alternative triflyloxycarbenium ion **7** or the triflyloxyoxonium ion **10**. Theoretical calculations using molecular mechanics (PM3 and AM1) within Hyperchem v7.51 program show that **7** is more stable than intermediate **10** (see Table 1 of Supporting Information). Intermediate **7** is trapped by the thiocyanate forming a nitrilium ion **8**, which reacts with a second molecule of thiocyanate. Elimination of TfOH and a subsequent cyclization affords the olefinic intermediate **9** which finally gives the pyrimidine **4**.

In the alternate path, intermediate **10** undergoes nucleophilic displacement of an alkyltriflate molecule (R^2OTf) by methyl thiocyanate to form the intermediate **11**. In this case, the absence of the TfO leaving group precludes the formation of a double bond (as in **9**); as a consequence, the involvement of a second molecule of nitrile is not needed. Basic hydrolysis during the work-up of the reaction leads to the formation of the thiocarbamate **5**. The elimination of R^2OTf was demonstrated by the finding that either ethyl acetate or propyl acetate affords the same thiocarbamate **5a** (Table 1). Apparently the nature of the R^2 group does not play any role in this process.

The exclusive formation of the carbamates **5** when R^1 = H (alkyl acetates) can be explained assuming the relative



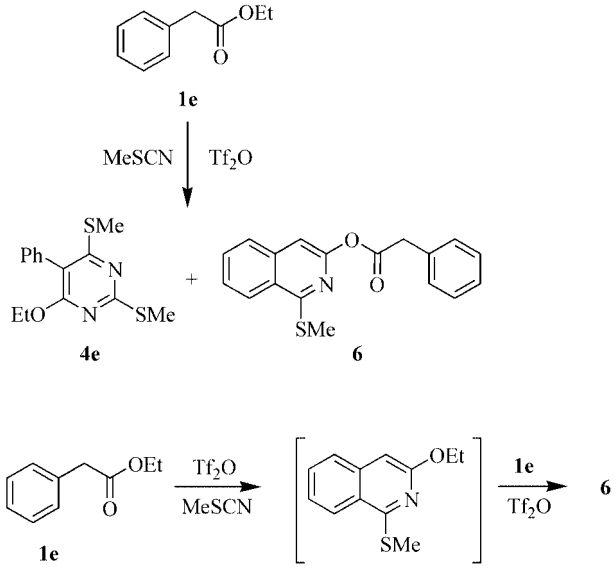
Scheme 3.

instability of the olefinic intermediate **9** compared with its counterparts when R^1 is an alkyl or phenyl group. Similar results were found in the study of the regioselectivity of the reaction of aliphatic ketones and nitriles.[22]

On the other hand, the differences found in the product distributions when nitriles or thiocyanates are used are likely to be controlled by the relative rates of reaction of these reagents with the intermediates **7** and **10**. Hence, a less nucleophilic reagent leads to both pyrimidines and carbamates.

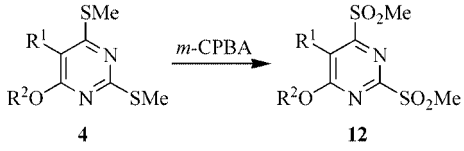
It is interesting to note that the reaction of ethyl phenylacetate (**1e**) with methyl thiocyanate affords an isoquinoline derivative **6** as well as the corresponding alkoxypyrimidine **4e** (Scheme 4). Isoquinolines are the main products of the reaction of alkyl phenylacetates with nitriles.[23] In this case, the ethoxy isoquinoline formed from ring closure of the intermediate **11** undergoes Tf_2O-catalyzed transesterification with a second molecule of **1e**, affording **6**.

The alkoxypyrimidines (**4**) and *S*-methylthio carbamates (**5**) were easily separated by column chromatography. This reaction can be used as a versatil tool to prepare two different classes of substances. The thiomethyl group attached to a pyrimidine ring can be only removed under harsh conditions.[24] However, the thiomethyl group can be easily oxidized to methylsulfonyl, which is a better leaving group.



Scheme 4.

Oxidation of the alkoxypyrimidines (**4**) with *m*CPBA affords the corresponding 4-alkoxy-2,6-bis(methylsulfonyl)-pyrimidines (**12**) (Scheme 5 and Table 2).



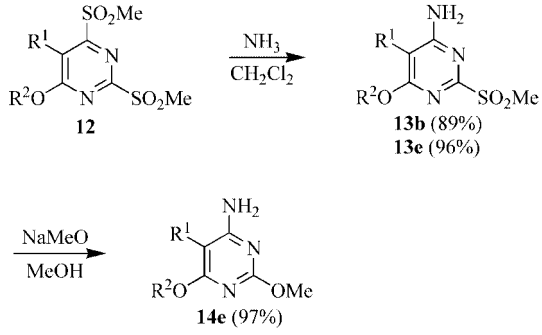
Scheme 5.

Table 2. 4-Alkoxy-2,6-bis(methylsulfonyl)pyrimidines **12**.

Compound	Yield (%)[a]
12b	91
12c	96
12d	86
12e	95
12f	85

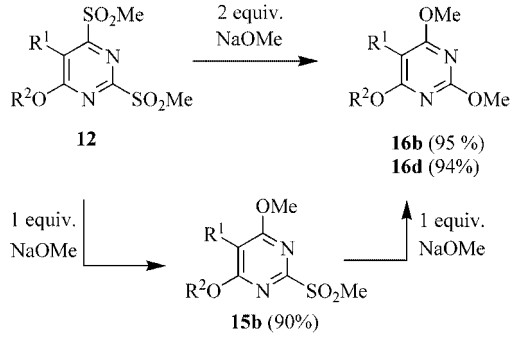
[a] Yield of isolated product.

Methylsulfonyl pyrimidines are excellent synthetic intermediates because they can undergo nucleophilic substitution with a variety of reagents under mild conditions.[25] The displacement of one or both methylsulfonyl groups can be controlled either by the reaction conditions or by the amount of the corresponding reagent. The methylsulfonyl group at the C6 position can be first removed while the substitution at the C2 position requires more rigorous conditions. Thus, the reaction of **12** with ammonia affords the corresponding aminopyrimidines **13**. The remaining methylsulfonyl group cannot be removed with ammonia, but it can be easily displaced with sodium methoxide leading to the formation of 4-amino-2-methoxypyrimidines **14** (Scheme 6).



Scheme 6.

The reaction of **12** with an equimolecular amount of sodium methoxide produces the corresponding methoxy derivative **15**, which can be converted into the dimethoxy derivative **16** by reaction with an additional equivalent of sodium methoxide. The direct conversion of **12** into the 2,6-dimethoxyderivative **15** is easily carried out using directly two equivalents of the reagent (Scheme 7).



Scheme 7.

In summary, we report a new synthetic route for the preparation of a variety of substituted aminoalkoxy-, di- and trialkoxypyrimidines based on the reaction of esters and methyl thiocyanate. This reaction also permits the preparation of thiocarbamates from acetates.

Experimental Section

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.[26,27] Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by thin-layer chromatography. Column chromatography was performed using silica gel 60. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The IR spectra were measured with a Shimadzu FTIR 8300 instrument. NMR spectra were recorded with a Bruker DPX 300 and Bruker Avance AV 500 at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C and 500 MHz for ^{1}H and 125.72 MHz for ^{13}C, respectively. Chemical shifts are given in δ units (ppm) to residual $CHCl_3$ (7.26 and 77.0 ppm, respectively) and DMSO (2.50 and 39.5 ppm, respectively). *J* values are given in Hz. NMR assignments were accomplished with help of DEPT and 2D spectra. Mass spectra (EI) were recorded with a HP 5989A quadrupole instrument at 70 eV with a source temperature of 200 °C. Mass spectra (ESI) were car-

ried out with a Bruker Esquire ion-trap spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 CHN apparatus.

General Procedure for the Preparation of 4-Alkoxy-2,6-bis(methylthio)pyrimidines 4: To a solution containing methyl thiocyanate (2.19 g, 30.0 mmol) and the corresponding ester (10.0 mmol) in 20 mL of dichloromethane at –78 °C was added dropwise a solution of triflic anhydride (4.23 g, 15.0 mmol) in 20 mL of dichloromethane. The reaction mixture was stirred at this temperature for 1 h and allowed to stand at 0 °C for 4 d. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was washed with brine and dried with magnesium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography using hexane/ethyl acetate, 8:2 as eluent. The crude product was recrystallized.

4-Ethoxy-5-methyl-2,6-bis(methylthio)pyrimidine (4b): Following the general procedure, the reaction with the ethyl propanoate **1b** gave 1.80 g of a white solid, 78% yield; m.p. 51–52 °C (MeOH). $C_9H_{14}N_2OS_2$ (230.3): calcd. C 46.93, H 6.13, N 12.16, S 27.84; found C 46.85, H 6.03, N 12.09, S 27.71. ESI-MS: *m/z* = 231 $[M+H]^+$, 253 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.37 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 2.02 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3S), 2.57 (s, 3 H, CH_3S), 4.39 (q, J = 7.2 Hz, 2 H, CH_3CH_2). ^{13}C NMR ($CDCl_3$): δ = 9.9 (CH_3), 13.0 (CH_3S), 14.1 (CH_3S), 14.5 (CH_3CH_2), 62.5 (CH_2), 109.0 (C5), 165.8 (C6), 166.8 (C4), 167.1 (C2). IR (KBr): $\tilde{\nu}$ = 2980, 1554, 1340, 1053 cm^{-1}.

5-Butyl-4-ethoxy-2,6-bis(methylthio)pyrimidine (4c): Following the general procedure, the reaction with ethyl hexanoate **1c** gave 1.14 g of a white solid, 42% yield; m.p. 47–48 °C (MeOH). $C_{12}H_{20}N_2OS_2$ (272.4): calcd. C 52.90, H 7.40, N 10.28, S 23.54; found C 52.79, H 7.33, N 10.13, S 23.45. EI-MS: *m/z* (%) = 272 (57) $[M^+]$, 257 (43) $[M - CH_3]$, 243 (41) $[M - C_2H_5]$, 229 (100) $[M - C_3H_7]$. ESI-MS: *m/z* = 273 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.1 Hz, 3 H, CH_3CH_2), 1.25–1.27 (m, 4 H, CH_2), 1.35 (t, J = 7.1 Hz, 3 H, CH_3CH_2O), 2.50 (t, J = 7.1 Hz, 2 H, CH_2CH_2) 2.54 (s, 6 H, CH_3S), 4.39 (q, J = 7.2 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3S), 13.8 (CH_3CH_2), 14.0 (CH_3S), 14.4 (CH_3CH_2O), 22.6 (CH_2), 24.6 (CH_2), 62.3 (CH_2O), 113.0 (C5), 165.3 (C6), 166.8 (C4), 166.9 (C2). IR (KBr): $\tilde{\nu}$ = 2955, 2924, 1551, 1340 cm^{-1}.

4-Ethoxy-2,6-bis(methylthio)-5-octylpyrimidine (4d): Following the general procedure, the reaction with ethyl decanoate **1d** gave 1.48 g of a white solid, 45% yield; m.p. 29–30 °C (MeOH). $C_{16}H_{28}N_2OS_2$ (328.5): calcd. C 58.49, H 8.59, N 8.53, S 19.52; found C 58.32, H 8.43, N 8.39, S 19.40. EI-MS: *m/z* (%) = 328 (42) $[M^{+\cdot}]$, 313 (61) $[M - CH_3]$, 281 (70) $[M - CH_3S]$, 243 (32) $[M - C_6H_{13}]$, 229 (100) $[M - C_7H_{15}]$. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.28–1.48 (m, 15 H, 1 CH_3, 6 CH_2), 2.49 (t, J = 7.3 Hz, 2 H, CH_2CH_2) 2.54 (s, 3 H, CH_3S), 2.56 (s, 3 H, CH_3S), 4.40 (q, J = 7.2 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 13.1 (CH_3S), 14.0 (CH_3S), 14.1 (CH_3CH_2), 14.5 (CH_3CH_2O), 22.6 (CH_2), 25.0 (CH_2), 27.5 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 62.4 (CH_2O), 113.2 (C5), 165.3 (C6), 166.7 (C4), 166.9 (C2). IR (KBr): $\tilde{\nu}$ = 2925, 1551, 1529, 1340, 1049 cm^{-1}.

4-Ethoxy-5-phenyl-2,6-bis(methylthio)pyrimidine (4e): Following the general procedure, the reaction with ethyl phenylacetate **1e** gave 2.07 g of a white solid, 71% yield; m.p. 83–84 °C (MeOH). $C_{14}H_{16}N_2OS_2$ (202.4): calcd. C 57.50, H 5.52, N 9.58, S 21.93; found C 57.42, H 5.39, N 9.45, S 21.79. EI-MS: *m/z* (%) = 292 (100) $[M^{+\cdot}]$, 263 (15) $[M - C_2H_5]$, 231 (26). ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3CH_2), 2.48 (s, 3 H, CH_3S), 2.60 (s, 3 H, CH_3S), 4.39 (q, J = 7.1 Hz, 2 H, CH_2O), 7.28–7.44 (m, 5 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 13.4 (CH_3S), 14.1 (CH_3S), 14.3 (CH_3CH_2), 62.6 (CH_2O), 113.7 (C5), 128.0 (arom.), 128.3 (arom.), 130.2 (arom.), 132.5 (arom.), 164.4 (C6), 168.0 (C4), 168.8 (C2). IR (KBr): $\tilde{\nu}$ = 1541, 1514, 1342, 1042 cm^{-1}.

4-Butoxy-5-methyl-2,6-bis(methylthio)pyrimidine (4f): Following the general procedure, the reaction with the butyl propanoate **1f** gave 1.80 g of a yellow undistillable oil, 69% yield. $C_{11}H_{18}N_2OS_2$ (258.4): calcd. C 51.13, H 7.02, N 10.84, S 24.82; found C 50.99, H 6.90, N 10.77, S 24.69. ESI-MS: *m/z* (%) = 259 $[M+H]^+$. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.44 (sext, 2 H, J = 7.4 Hz, 2 H, $CH_3CH_2CH_2$), 1.73 (quint, J = 6.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.01 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3S), 2.55 (s, 3 H, CH_3S), 4.33 (t, J = 6.5 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 9.6 (CH_3), 12.7 (CH_3CH_2), 13.6 (CH_3S), 13.8 (CH_3S), 19.0 (CH_2), 31.0 (CH_2), 66.1 (CH_2O), 108.0 (C5), 165.0 (C6), 166.6 (C4), 166.8 (C2). IR (film): $\tilde{\nu}$ = 2961, 1553, 1533, 1344 cm^{-1}.

***S*-Methyl *N*-Acetylthiocarbamate (5a):** Following the general procedure, the reaction with ethyl acetate gave 0.77 g of a pale yellow solid 58% yield (from propyl acetate 51% yield); m.p. 146–147 °C ($CHCl_3$/hexane).From propyl acetate, 51% yield. $C_4H_7NO_2S$ (133.1): calcd. C 36.08, H 5.30, N 10.52, S 24.08; found C 35.93, H 5.23, N 10.44, S 23.92. EI-MS: *m/z* (%) = 133 $[M^{+\cdot}$, not observed], 90 (10) $[M - CH_3CO]$, 45 (14) $[CH_3S^+]$, 43 (100) $[CH_3CO^+]$. ^{1}H NMR ([D$_6$]DMSO): δ = 2.31 (s, 3 H, CH_3S), 2.37 (s, 3 H, CH_3), 8.53 (br. s, 1 H, NH). ^{13}C NMR ([D$_6$]DMSO): δ = 11.8 (CH_3S), 23.7 (CH_3), 169.4 (CO), 170.0 (COS) IR (KBr): $\tilde{\nu}$ = 3142, 1651, 1257, 1184 cm^{-1}.

***S*-Methyl *N*-Hexanoylthiocarbamate (5d):** Following the general procedure, the reaction with ethyl hexanoate **1c** gave 0.81 g of a white solid 43% yield; m.p. 80–81 °C (MeOH). $C_8H_{15}NO_2S$ (189.2): calcd. C 50.76, H 7.99, N 7.40, S 16.94; found C 50.66, H 7.86, N 7.29, S 16.77. ESI-MS: *m/z* (%) = 212 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.28–1.36 (m, 4 H, 2CH_2), 1.67 (q, J = 7.4 Hz, 2 H, $CH_2CH_2CH_2$), 2.34 (s, 3 H, CH_3S), 2.48 (t, J = 7.4 Hz, 2 H, CH_2CO) 8.17 (br. s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 12.5 (CH_3S), 13.8 (CH_3), 22.3 (CH_2), 24.1 (CH_2), 31.2 (CH_2), 37.0 (CH_2), 170.5 (COS), 172.6 (CO) IR (KBr): $\tilde{\nu}$ = 3192, 1717, 1649, 1257, 1223 cm^{-1}.

***S*-Methyl *N*-Decanoylthiocarbamate (5d):** Following the general procedure, the reaction with ethyl decanoate gave **1d** 1.03 g of a pale yellow solid 42% yield; m.p. 88–89 °C (MeOH). $C_{12}H_{23}NO_2S$ (245.3): calcd. C 58.74, H 9.45, N 5.71, S 13.07; found C 58.64, H 9.33, N 5.64, S 12.98. ESI-MS: *m/z* (%) = 246 $[M+H]^+$, 268 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.26–1.36 (m, 12 H, 6CH_2), 1.66 (q, J = 7.3 Hz, 2 H, $CH_2CH_2CH_2$), 2.34 (s, 3 H, CH_3S), 2.48 (t, J = 7.3 Hz, 2 H, CH_2CO) 8.76 (br. s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 12.5 (CH_3S), 14.0 (CH_3), 22.6 (CH_2), 24.4 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.9 (CH_2), 171.4 (COS), 173.1 (CO). IR (KBr): $\tilde{\nu}$ = 3258, 1728, 1163, 1149 cm^{-1}.

1-(Methylthio)isoquinolin-3-yl Phenylacetate (6): Following the general procedure, the reaction with ethyl phenylacetate **1e** gave 0.30 g of a yellow solid 19% yield; m.p. 79–80 °C (EtOH). $C_{18}H_{15}NO_2S$ (309.3): calcd. C 69.88, H 4.89, N 4.53, S 10.36; found C 69.70, H 4.70, N 4.47, S 10.25. EI-MS: *m/z* (%) = 309 (6) $[M^{+\cdot}]$, 191 (100), 91 (40) $[C_7H_7^+]$. ^{1}H NMR ($CDCl_3$): δ = 2.69 (s, 3 H, CH_3S), 4.00 (s, 2 H, CH_2), 7.08 (s, 1 H, H4), 7.36 (t, J = 7.4 Hz, 1 H, H4′), 7.42 (t, J = 7.4 Hz, 2 H, H3′, H5′), 7.48 (d, J = 7.4 Hz, 2 H, H2′, H6′), 7.53 (t, J = 7.7 Hz, 1 H, H6), 7.66 (t, J = 7.7 Hz, 1 H, H7), 7.74 (d, J = 7.7 Hz, 1 H, H5), 8.19 (d, J = 7.7 Hz, 1 H, H8). ^{13}C NMR ($CDCl_3$): δ = 13.0 (CH_3S), 41.4 (CH_2), 106.2 (C4), 124.5 (C8), 125.9 (C4a), 126.5 (C6), 127.1 (C5), 127.3 (C4′), 128.7

(C3′, C5′), 129.4 (C2′), 130.7 (C7), 133.4 (C1′), 137.7 (C8a), 152.9 (C3), 160.8 (C1), 169.9 (CO). IR (KBr): $\tilde{\nu}$ = 1749, 1551, 1227, 1142 cm^{-1}.

General Procedure for the Preparation of 4-Alkoxy-2,6-bis(methylsulfonyl)pyrimidines 12: To a stirred solution of the corresponding 4-alkoxy-2,6-bis(methylthio)pyrimidine **4** (4.0 mmol) in 15 mL of dichloromethane was added slowly a solution containing *m*CPBA (3.12 g, 18 mmol) in 20 mL of dichloromethane. The mixture was stirred at room temperature for 4 h. An aqueous solution of sodium thiosulfate (5%) was then added, shaked and the layers separated. The aqueous layer was extracted with dichloromethane and the combined organic layers washed with sodium hydrogen carbonate, brine and dried with magnesium sulfate. The solvent was removed in vacuo and the residue was purified by recrystallization.

4-Ethoxy-5-methyl-2,6-bis(methylsulfonyl)pyrimidine (12b): Following the general procedure, the reaction with **4b** gave 1.07 g of a white solid, 91% yield; m.p. 130–131 °C (MeOH). $C_9H_{14}N_2O_5S_2$ (294.3): calcd. C 36.72, H 4.79, N 9.52, S 21.79; found C 36.59, H 4.69, N 9.39, S 21.66. EI-MS: *m*/*z* (%) = 294 (21) [$M^{+\cdot}$], 266 (41) [M – C_2H_4], 250 (100) [M – C_2H_4O], 215 (15) [M – CH_3SO_2]. ^{1}H NMR ($CDCl_3$): δ = 1.50 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 2.59 (s, 3 H, CH_3), 3.32 (s, 3 H, CH_3SO_2), 3.41 (s, 3 H, CH_3SO_2), 4.64 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2). ^{13}C NMR ($CDCl_3$): δ = 10.2 (CH_3), 14.0 (CH_2) 39.0 (CH_3SO_2), 40.0 (CH_3SO_2), 65.9 (CH_2), 120.5 (C6), 161.6 (C5), 162.6 (C2), 170.7 (C4). IR (KBr): $\tilde{\nu}$ = 1560, 1431, 1346, 1313, 1136 cm^{-1}.

5-Butyl-4-ethoxy-2,6-bis(methylsulfonyl)pyrimidine (12c): Following the general procedure, the reaction with **4c** gave 1.29 g of a white solid, 96% yield; m.p. 108–109 °C (MeOH). $C_{12}H_{20}N_2O_5S_2$ (336.4): calcd. C 42.84, H 5.99, N 8.33, S 19.06; found C 42.70, H 5.81, N 8.22, S 18.95. EI-MS: *m*/*z* (%) = 336 (18) [$M^{+\cdot}$], 321 (15) [M – CH_3], 307 (100) [M – C_2H_5], 279(46) [M – C_4H_9], 257 (50) [M – CH_3SO_2]. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 1.38–1.62 (m, 4 H, CH_2), 1.46 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 3.02 (t, *J* = 7.1 Hz, 2 H, CH_2CH_2) 3.30 (s, 3 H, CH_3SO_2), 3.37 (s, 3 H, CH_3SO_2), 4.61 (q, *J* = 7.2 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 13.54 ($CH_3CH_2CH_2$), 13.91 (CH_3CH_2O), 22.8 (CH_2), 24.2 (CH_2), 30.5 (CH_2), 39.0 (CH_3SO_2), 40.2 (CH_3SO_2), 65.7 (CH_2O), 125.2 (C5), 161.6 (C6), 164.5 (C2), 170.7 (C4). IR (KBr): $\tilde{\nu}$ = 2961, 1558, 1344, 1317, 1140 cm^{-1}.

4-Ethoxy-2,6-bis(methylsulfonyl)-5-octylpyrimidine (12d): Following the general procedure, the reaction with **4d** gave 1.35 g of a white solid, 86% yield; m.p. 101–102 °C (MeOH). $C_{16}H_{28}N_2O_5S_2$ (392.5): calcd. C 48.96, H 7.19, N 7.14, S 16.34; found C 48.82, H 7.09, N 7.06, S 14.40. EI-MS: *m*/*z* (%) = 392 (5) [$M^{+\cdot}$], 377 (7) [M – CH_3], 313 (100) [M – CH_3SO_2]. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.6 Hz, 3 H, CH_3CH_2), 1.27–1.36 (m, 10 H, $5CH_2$), 1.48 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O) 1.60 (m, 2 H, $CH_2CH_2CH_2$), 3.03 (t, *J* = 7.6 Hz, 2 H, CH_2CH_2), 3.32 (s, 3 H, CH_3SO_2), 3.39 (s, 3 H, CH_3SO_2), 4.64 (q, *J* = 7.1 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3CH_2O), 14.1 (CH_3CH_2), 22.6 (CH_2), 24.6 (CH_2), 28.5 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 39.1 (CH_3SO_2), 40.3 (CH_3SO_2), 65.8 (CH_2O), 125.4 (C5), 161.7 (C6), 162.7 (C2), 171.0 (C4). IR (KBr): $\tilde{\nu}$ = 1556, 1431, 1344, 1310, 1140 cm^{-1}.

4-Ethoxy-2,6-bis(methylsulfonyl)-5-phenylpyrimidine (12e): Following the general procedure, the reaction with **4e** gave 1.35 g of a white solid, 95% yield; m.p. 137–138 °C (MeOH). $C_{14}H_{16}N_2O_5S_2$ (356.4): calcd. C 47.18, H 4.52, N 7.86, S 17.99; found C 47.11, H 4.40, N 7.78, S 17.79. EI-MS: *m*/*z* (%) = 356 (100) [$M^{+\cdot}$], 328 (44) [M – C_2H_4], 277 (28) [M – SO_2CH_3]. ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 3.29 (s, 3 H, CH_3SO_2), 3.39 (s, 3 H, CH_3SO_2), 4.60 (q, *J* = 7.1 Hz, 2 H, CH_2O), 7.37–7.51 (m, 5 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3CH_2), 39.1 (CH_3SO_2), 40.5 (CH_3SO_2), 66.2 (CH_2O), 123.5 (C5), 127.5 (arom.), 128.1 (arom.), 129.7 (arom.), 129.8 (arom.), 162.9 (C6), 170.2 (C4, C2). IR (KBr): $\tilde{\nu}$ = 1437, 1342, 1317, 1144 cm^{-1}.

4-Butoxy-5-methyl-2,6-bis(methylsulfonyl)pyrimidine (12f): Following the general procedure, the reaction with **4f** gave 1.04 g of a white solid, 81% yield; m.p. 89–90 °C (MeOH). $C_{11}H_{18}N_2O_5S_2$ (322.4): calcd. C 40.98, H 5.63, N 8.69, S 19.89; found C 40.80, H 5.55, N 8.59, S 19.87. ESI-MS: *m*/*z* (%) = 323 [M + H]$^+$. ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2), 1.49 (sext, 2 H, *J* = 7.3 Hz, 2 H, $CH_3CH_2CH_2$), 1.84 (quint, *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2$), 2.58 (s, 3 H, CH_3), 3.32 (s, 3 H, CH_3SO_2), 3.41 (s, 3 H, CH_3SO_2), 4.56 (t, *J* = 6.6 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 10.0 (CH_3), 13.5 (CH_3CH_2), 19.0 (CH_2), 30.2 (CH_2), 38.9 (CH_3SO_2), 39.9 (CH_3SO_2), 69.5 (CH_2O), 120.3 (C5), 161.5 (C6), 162.4 (C2), 170.7 (C4). IR (KBr): $\tilde{\nu}$ = 2953, 1566, 1304, 1144 cm^{-1}.

General Procedure for the Preparation of 4-Aminopyrimidines 13: A continuous stream of ammonia was bubbled through a solution of the corresponding bis(methylsulfonyl)pyrimidine **12** (1.5 mmol) in 25 mL of dichloromethane at room temperature. After 16 h, the solvent was distilled off, the residue washed with water and purified by recrystallization.

6-Ethoxy-5-methyl-2-(methylsulfonyl)pyrimidin-4-amine (13b): Following the general procedure, the reaction with **11b** gave 0.31 g of a white solid, yield 89%; m.p. 135–136 °C (MeOH). $C_8H_{13}N_3O_3S$ (231.2): calcd. C 41.55, H 5.76, N 18.17, S 13.86; found C 41.40, H 5.66, N 18.11, S 13.70. EI-MS: *m*/*z* (%) = 231 (16) [$M^{+\cdot}$], 216 (6) [M – CH_3], 187 (100) [M – C_2H_4O]. ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 2.32 (s, 3 H, CH_3), 3.23 (s, 3 H, CH_3SO_2), 4.37 (q, *J* = 7.1 Hz, 2 H, CH_2O), 5.00 (br. s, 2 H, NH_2). ^{13}C NMR ($CDCl_3$): δ = 8.4 (CH_3), 14.1 (CH_3CH_2), 39.6 (CH_3SO_2), 62.5 (CH_2O), 101.3 (C5), 160.4 (C4), 162.6 (C2), 169.3 (C6). IR (KBr): $\tilde{\nu}$ = 3516, 3194, 1425, 1344, 1311, 1240 cm^{-1}.

6-Ethoxy-2-(methylsulfonyl)-5-phenylpyrimidin-4-amine (13e): Following the general procedure, the reaction with **12e** gave 0.42 g of a white solid, 96% yield; m.p. 150–151 °C (MeOH). $C_{13}H_{15}N_3O_3S$ (293.3): calcd. C 53.23, H 5.15, N 14.32, S 10.93; found C 53.15, H 4.99, N 14.22, S 10.84. EI-MS: *m*/*z* (%) = 293 (100) [$M^{+\cdot}$], 278 (4) [M – CH_3], 265 (11) [M – C_2H_4]. ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 3.06 (s, 3 H, CH_3SO_2), 4.34 (q, *J* = 7.1 Hz, 2 H, CH_2O), 5.24 (br. s, 2 H, NH_2), 7.30–7.42 (m, 5 H, Ar-H). ^{13}C NMR ([D_6]DMSO): δ = 14.0 (CH_3CH_2), 40.3 (CH_3SO_2), 62.6 (CH_2O), 107.3 (C5), 127.3 (arom.), 130.9 (arom.), 131.0 (arom.), 161.2 (C4), 162.8(C2), 168.5 (C6). IR (KBr): $\tilde{\nu}$ = 3161, 1583, 1302, 1238, 1207, 1059 cm^{-1}.

General Procedure for the Preparation of Methoxypyrimidines 14, 15 and 16: solution containing 1.5 mmol of the corresponding mono or bis(methylsulfonyl)pyrimidines and 1.5 mmol of sodium methoxide (4.0 mmol for the double substitution) in 20 mL of dry methanol was refluxed for 15 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization.

6-Ethoxy-2-methoxy-5-phenylpyrimidin-4-amine (14e): Following the general procedure, the reaction of **12e** gave 0.36 g of a white solid, 97% yield; m.p. 110–111 °C (MeOH). $C_{13}H_{15}N_3O_2$ (245.2): calcd. C 63.66, H 6.16, N 17.13; found C 63.53, H 6.08, N 17.10. EI-MS: *m*/*z* (%) = 245 (100) [$M^{+\cdot}$], 230 (17) [M – CH_3], 228 (18) [M – NH_3]. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H,

CH_3CH_2), 3.90 (s, 3 H, CH_3O), 4.39 (q, J = 7.1 Hz, CH_2O), 5.47 (br. s, 2 H, NH_2), 7.30–7.37 (m, 5 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3), 54.1 (CH_3O), 62.7 (CH_2O), 96.2 (C5), 126.6 (arom.), 127.6 (arom.), 130.8 (arom.), 131.7 (arom.), 159.9 (C4), 167.5 (C2), 168.1 (C6). IR (KBr): $\tilde{\nu}$ = 3481, 3337, 1560, 1553, 1373 cm^{-1}.

4-Ethoxy-5-methyl-2-(methylsulfonyl)-6-methoxypyrimidine (15b): Following the general procedure, the reaction of **11b** gave 0.33 g of a white solid, 90% yield; m.p. 107–108 °C (MeOH). $C_9H_{14}N_2O_4S$ (246.2): calcd. C 43.98, H 5.73, N 11.37, S 13.02; found C 43.88, H 5.60, N 11.20, S 12.90. EI-MS: m/z (%) = 246 (22) [$M^{+\cdot}$], 218 (13) [M – C_2H_4], 202 (100) [M – C_2H_4O]. ^1H NMR ($CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, CH_3CH_2), 2.40 (s, 3 H, CH_3), 3.32 (s, 3 H, CH_3SO_2), 3.97 (s, 3 H, CH_3O), 4.48 (q, J = 7.1 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 9.0 (CH_3), 14.2 (CH_3CH_2), 39.9 (CH_3SO_2), 55.1 (CH_3O), 64.1 (CH_2O), 109.5 (C5), 162.3, 162.8, 171.4 (C4). IR (KBr): $\tilde{\nu}$ = 1589, 1556, 1391, 1371, 1308, 1132 cm^{-1}.

4-Ethoxy-2,6-dimethoxy-5-methylpyrimidine (16b): Following the general procedure, the reaction of **11b** or **14b** gave 0.28 g of a pale yellow solid, 95% yield; m.p. 39–40 °C (MeOH). $C_9H_{14}N_2O_3$ (198.2): calcd. C 54.53, H 7.12, N 14.13; found C 54.44, H 7.10, N 14.09. ESI-MS: m/z (%) = 199 $[M+H]^+$. ^1H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, CH_3CH_2), 1.88 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3O), 3.91 (s, 3 H, CH_3O), 4.36 (q, J = 7.1 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 6.6 (CH_3), 14.4 (CH_3CH_2), 53.7 (CH_3O), 54.0 (CH_3O), 62.3 (CH_2O), 92.5 (C5), 162.0 (C2), 169.0 (C6), 169.4 (C4). IR (KBr): $\tilde{\nu}$ = 2990, 1611, 1583, 1381, 1155 cm^{-1}.

4-Ethoxy-2,6-dimethoxy-5-octylpyrimidine (16d): Following the general procedure, the reaction of **11d** gave 0.42 g of a pale yellow undistillable oil 94% yield. $C_{16}H_{28}N_2O_3$ (296.4): calcd. C 64.83, H 9.52, N 9.45; found C 64.70, H 9.40, N 9.34. EI-MS: m/z (%) = 296 (14) [$M^{+\cdot}$], 265 (7) [M – CH_3], 251 (17) [M – C_2H_5O], 197 (100) [M – C_8H_{17}]. ^1H NMR ($CDCl_3$): δ = 0.85 (t, J = 7.6 Hz, $CH_3CH_2CH_2$), 1.24 (m, 12 H, $6CH_2$), 1.33 (t, J = 7.1 Hz, CH_3CH_2O), 2.38 (t, J = 7.6 Hz, 2 H, CH_2), 3.89 (s, 3 H, CH_3O), 3.90 (s, 3 H, CH_3O), 4.36 (q, J = 7.1 Hz, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 14.6 (CH_3), 21.5 (CH_2), 22.6 (CH_2), 28.5 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 53.8 (CH_3O), 54.2 (CH_3O) 62.2 (CH_2O), 97.8 (C5), 162.1 (C2), 169.15, 169.5. IR (film): $\tilde{\nu}$ = 2926, 1582, 1462, 1381, 1142 (cm^{-1}).

Supporting Information (see also the footnote on the first page of this article): ^1H NMR, ^{13}C NMR and DEPT spectra of compounds **4b-f**, **5a**, **5c**, **5d**, **6**, **11b-f**, **12b**, **12e**, **13e**, **14b**, **15b** and **15d**.

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