Reagents for new heteroannelation reactions. Part VI. 2-(Methylsulfanyl)-1,4,5,6-tetrahydropyrimidine

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Dedicated to Prof. Fritz Sauter on the occasion of his 70th birthday
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Abstract
The reaction of heteroaromatic 2-aminoesters and 2-aminonitriles with 2-(methylthio)-1,4,5,6-tetrahydropyrimidine results in annelation of a pyrimido[1,2-a]pyrimidine moiety in a one-pot process, providing access to a number of predominantly novel tri- and tetracyclic hetero-systems.

Keywords: 2-(Methylsulfanyl)-1,4,5,6-tetrahydropyrimidine, fused pyrimido[1,2-a]pyrimidines, fused S,N-heterocycles

Introduction
In recent papers we have reported on the one-pot annelation of a pyrimidine ring to 2-aminoesters using compounds of the versatile N-[bis(methylthio)methylene]amino type (BMMA-type)² (Scheme 1) as well as on the extension of this methodology towards cyclic analogs of the BMMA reagents, resulting in double-reactions of imidazo[1,2-a]pyrimido,¹ thiazolo[2,3-b]pyrimido,³ and pyrimido[2,1-b]thiazino⁴ moieties.
Scheme 1

In addition, 2-aminonitriles were employed as starting materials and afforded the corresponding imino derivatives (Scheme 2).

Scheme 2

In continuation of the above-mentioned work with cyclic reagents this paper describes the utilization of 2-(methylsulfanyl)-1,4,5,6-tetrahydropyrimidine (1) within the BMMA strategy, thus expanding the scope of this reactions towards the annelation of a pyrimido[1,2-\(a\)]pyrimidine unit.

Results and Discussion

The reaction of a variety of heteroaromatic aminoesters and aminonitriles with 1 furnished the desired tri- and tetracyclic fusion products 2, 3 and 4, 5, respectively (Scheme 3). In a series of experiments, solvent and temperature conditions were optimized. Heating the starting materials in HMPA to 150 °C or without solvent to 170 °C for several hours gave best results.
Scheme 3

The reaction of 1 with a number of monocyclic heterocycles with vicinal amino and ester functionalities gave the tricyclic oxo compounds 2, and from the reaction of 1 with accordingly substituted heterocyclic amino nitriles the imino derivatives 3 were obtained.

Cycloalkane- and heterocycle-fused thiophenes with 2-amino and 3-ester or 3-nitrile functionalities as well as 2-amino-4,5,6,7-tetrahydrobenzofuran-3-carbonitrile were the suitable starting materials (easily accessible from suitable cyclic ketones via the
Gewald reaction; references are provided in the Experimental part) for the preparation of the corresponding tetracyclic oxo and imino compounds 4 and 5, respectively.

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Compound 4b has already been prepared by a similar reaction\(^5\) in very poor yield, and was identified only by its molecular ion peak in a mass spectroscopic analysis. In contrast, the method described here provides easy, one-step access to polynuclear heterocyclic compounds in fair to good yields starting from relatively simple substrates.

**Experimental Section**

**General Procedures.** Melting points (mp) were determined on a Kofler hot stage apparatus. \(^1\)H and \(^13\)C NMR spectra were recorded on a Bruker AC 200 spectrometer (200 MHz for \(^1\)H; TMS as internal standard, DMSO-\(d_6\) as solvent, \(\delta\) values in ppm). Elementary analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. J. Theiner).

2-(Methylsulfanyl)-1,4,5,6-tetrahydropyrimidine (1) was prepared via a two-step procedure from 1,3-propanediamine and CS\(_2\) followed by methylation with methyl iodide (applying procedures originally published for 2-(methylsulfanyl)-2-imidazoline\(^6,7\)). Aminoesters and aminonitriles as starting materials were prepared according to known procedures (references given at the respective experiments).

**General procedure for the cyclization reaction**

2-(Methylsulfanyl)-1,4,5,6-tetrahydro-pyrimidine (1,56 g, 12 mmol) and the appropriate aminoester or aminonitrile (10 mmol) were heated under a nitrogen atmosphere either in HMPA (10 mL) to 150 °C or without solvent to 170 °C for a given period of time. After
cooling to room temperature crushed ice was added, and the mixture was stirred for 1 h. The separated product was collected by filtration and recrystallized from methanol (unless otherwise stated).

6,7,8,9-Tetrahydro-1-methylpyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(1H)-one (2a). From ethyl 5-amino-1-methylpyrazole-4-carboxylate,$^8$ neat at 170 °C; 2 h. Yield 1.40 g colorless crystals, 68%; mp 284 °C (ethanol/water 10:1); $^1$H NMR (DMSO-$d_6$): δ 8.00 (s, 1H), 7.70 (s, 1H), 3.80 (m, 2H), 3.60 (s, 3H), 3.30 (m, 2H), 1.90 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): δ 157.12 (s), 152.82 (s), 152.33 (s), 133.94 (d), 98.43 (s), 38.78 (t), 38.68 (t), 33.04 (t), 19.84 (q).

6,7,8,9-Tetrahydro-1-phenylpyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(1H)-one (2b). From ethyl 5-amino-1-phenylpyrazole-4-carboxylate; neat at 170 °C; 2 h. Yield 1.50 g colorless crystals, 56%; mp 275 °C; $^1$H NMR (DMSO-$d_6$): δ 8.30 (m, 2H), 8.00 (s, 1H), 7.50 (m, 2H), 7.30 (m, 1H), 3.90 (m, 2H), 3.30 (m, 2H), 1.90 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): δ 156.99 (s), 153.11 (s), 152.60 (s), 139.14 (d), 135.90 (s), 128.61 (2d), 125.40 (d), 120.41 (2d), 99.94 (s), 43.64 (t), 43.44 (t), 19.64 (t). Anal. Calcd. for C$_{14}$H$_{13}$N$_5$O (267.29): C, 62.91; H, 4.90; N, 26.20. Found: C, 62.62; H, 4.66; N, 26.06.

6,7,8,9-Tetrahydro-2-methylpyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(2H)-one (2c). From ethyl 3-amino-1-methyl-1H-pyrazole-4-carboxylate; neat at 170 °C; 2 h. Yield 0.82 g colorless crystals, 40%; mp 260 °C; $^1$H NMR (DMSO-$d_6$): δ 8.20 (s, 1H), 7.80 (s, 1H), 3.80 (m, 2H), 3.20 (m, 2H), 3.10 (s, 3H), 1.90 (m, 2H).

5,6,7,8-Tetrahydro-2-(methylsulfanyl)-10H-pyrimido[1,2-a]thiazolo[4,5-d]pyrimidin-10-one (2d). From ethyl 4-amino-2-(methylsulfanyl)thiazole-5-carboxylate; in HMPA at 150 °C; 5 h. Yield 1.76 g colorless crystals, 69%; mp 286 °C; $^1$H NMR (DMSO-$d_6$): δ 8.00 (s, 1H), 3.80 (m, 2H), 3.30 (m, 2H), 2.80 (s, 3H), 1.90 (m, 2H). Anal. Calcd for C$_9$H$_{10}$N$_4$OS$_2$ (254.32): C, 42.50; H, 3.96; N, 22.03. Found: C, 42.23; H, 3.66; N, 21.76.

5,6,7,8-Tetrahydro-2-(phenylamino)-10H-pyrimido[1,2-a]thiazolo[4,5-d]pyrimidin-10-one (2e). From ethyl 4-amino-2-(phenylamino)thiazole-5-carboxylate; in HMPA at 150 °C; 5 h. Yield 1.86 g colorless crystals, 62%; mp >320 °C; $^1$H NMR (DMSO-$d_6$): δ 7.90 (s, 1H), 7.70 (m, 2H), 7.40 (m, 2H), 7.00 (m, 1H), 3.90 (m, 2H), 3.30 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C$_{14}$H$_{13}$N$_5$OS (299.35): C, 56.17; H, 4.38; N, 23.40. Found: C, 55.72; H, 4.16; N, 22.97.

5,6,7,8-Tetrahydro-2-methyl-10H-oxazolo[5,4-d]pyrimido[1,2-a]pyrimidin-10-one (2f). From ethyl 5-amino-2-methyloxazole-4-carboxylate; neat at 170 °C; 45 min; purified by flash chromatography (SiO$_2$, chloroform/acetone 9:2). Yield 0.73 g colorless crystals, 35%; mp 304 °C; $^1$H NMR (DMSO-$d_6$): δ 8.10 (s, 1H), 3.90 (m, 2H), 3.30 (m, 2H), 1.90 (m, 2H).
2H), 2.40 (s, 3H), 1.90 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 164.60 (s), 155.47 (s), 155.11 (s), 152.21 (s), 109.64 (s), 39.49 (t), 39.08 (t), 19.24 (t), 13.75 (q). Anal. Calcd. for C$_9$H$_{10}$N$_4$O$_2$ (206.20): C, 52.42; H, 4.89; N, 27.17. Found: C, 52.14; H, 4.70; N, 26.88.

6,7,8,9-Tetrahydropyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(1H)-imine (3a). From 5-amino-1H-pyrazol-4-carbonitrile;$^{13}$ in HMPA; 5 h. Yield 0.88 g colorless crystals, 46%; mp 230 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.80 (s, 1H), 7.40 (s, 1H), 3.90 (m, 2H), 3.20 (m, 2H), 1.80 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 154.14 (s), 151.86 (s), 151.20 (s), 134.46 (d), 97.93 (s), 39.92 (t), 38.63 (t), 20.51 (t).

6,7,8,9-Tetrahydro-1-methylpyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(1H)-imine (3b). From 5-amino-1-methyl-1H-pyrazol-4-carbonitrile;$^{14}$ neat at 170 °C; 4 h. Yield 1.41 g yellow crystals, 69%; mp 200 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.80 (s, 1H), 7.60 (s, 1H), 7.20 (s, 1H), 3.90 (m, 2H), 3.60 (s, 3H), 3.20 (m, 2H), 1.90 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 153.78 (s), 151.90 (s), 149.30 (s), 133.94 (d), 97.98 (s), 39.85 (t), 38.58 (t), 33.86 (q), 20.34 (t).

6,7,8,9-Tetrahydro-2-methylpyrazolo[3,4-d]pyrimido[1,2-a]pyrimidin-4(2H)-imine (3c). From 3-amino-1-methyl-1H-pyrazole-4-carbonitrile;$^{15}$ neat at 170 °C; 2 h. Yield 0.98 g colorless crystals, 48%; mp 302 °C (ethanol/water 10:1); $^1$H NMR (DMSO-$d_6$): $\delta$ 8.00 (s, 1H), 7.50 (s, 1H), 7.20 (s, 1H), 3.90 (m, 2H), 3.70 (s, 3H), 3.20 (m, 2H), 1.90 (m, 2H). Anal. calcd for C$_9$H$_{12}$N$_6$ (204.23): C, 52.93; H, 5.92; N, 41.15; Found: C, 52.95; H, 5.86; N, 40.82.

5,6,7,8-Tetrahydro-2-(methylsulfanyl)-10H-pyrimido[1,2-a]thiazolo[4,5-d]pyrimidin-10-imine (3d). From 4-amino-2-(methylsulfanyl)thiazole-5-carbonitrile;$^{16}$ in HMPA at 150 °C; 4 h. Yield 1.52 g yellow crystals, 60%; mp 258 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.70 (s, 1H), 3.90 (m, 2H), 3.30 (m, 2H), 2.70 (s, 3H), 1.90 (m, 2H). Anal. Calcd. for C$_9$H$_{11}$N$_5$S$_2$ (253.34): C, 42.67; H, 4.3; N, 27.64. Found: C, 42.88; H, 4.02; N, 27.36.

1,3,4,7,8,9-Hexahydro-2H,6H-cyclopenta[4,5]thieno[2,3-d]pyrimido[1,2-a]pyrimidin-6-one (4a). From ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate;$^{17}$ in HMPA at 150 °C; 3 h. Yield 1.88 g colorless crystals, 76%; mp 310 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.80 (s, 1H), 3.90 (m, 2H), 3.30 (m, 2H), 2.90–2.70 (m, 4H), 2.30 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C$_{12}$H$_{13}$N$_3$OS (247.31): C, 58.28; H, 5.30; N, 16.99. Found: C, 58.06; H, 5.21; N, 16.78.

1,2,3,4,7,8,9,10-Octahydro-6H-[1]benzothieno[2,3-d]pyrimido[1,2-a]pyrimidin-6-one (4b). From ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate;$^{17}$ in HMPA at 150 °C; 3 h. Yield 2.17 g colorless crystals, 83%; mp 278 °C; H NMR (DMSO-$d_6$): $\delta$ 7.80 (s, 1H), 3.80 (m, 2H), 3.70 (m, 2H), 2.80 (m, 2H), 2.60 (m, 2H),
1.90 (m, 2H), 1.70 (m, 4H); $^{13}$C NMR (DMSO-$d_6$): δ 165.18 (s), 157.54 (s), 150.57 (s), 130.03 (s), 123.59 (s), 112.02 (s), 38.47 (t), 38.47 (t), 25.28 (t), 24.18 (t), 22.74 (t), 21.95 (t), 19.70 (t).

1,3,4,7,8,9,10,11-Octahydro-2H,6H-cyclohepta[4,5]thieno[2,3-$d$]pyrimido[1,2-$a$]pyrimidin-6-one (4c). From ethyl 2-amino-5,6,7,8-tetrahydro-4H-cyclohepta[$b$]thiophene-3-carboxylate; $^{18}$ in HMPA at 150 °C; 3 h. Yield 2.07 g pale yellow crystals, 75%; mp 240 °C; $^1$H NMR (DMSO-$d_6$): δ 7.70 (s, 1H), 3.80 (m, 2H), 3.30 (m, 2H), 3.10 (m, 2H), 2.60 (m, 2H), 1.90 (m, 2H), 1.80 (m, 2H), 1.50 (m, 4H).


1,2,3,4,7,8,9,10-Octahydro-9-(phenylmethyl)pyrido[4',3':4,5]thieno[2,3-$d$]pyrimido[1,2-$a$]pyrimidin-6-one (4d). From ethyl 2-amino-4,5,6,7-tetrahydro-6-(phenylmethyl)thieno[2,3-$c$]pyridine-3-carboxylate; $^{19}$ in HMPA at 150 °C; 3 h. Yield 2.79 g pale yellow crystals, 79%; mp 245 °C; $^1$H NMR (DMSO-$d_6$): δ 7.80 (s, 1H), 7.40–7.10 (m, 5H), 3.90 (m, 2H), 3.70 (s, 2H), 3.50 (s, 2H), 3.20 (m, 2H), 2.80 (m, 2H), 2.70 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C$_{19}$H$_{20}$N$_4$O$_3$ (352.45): C, 64.75; H, 5.72; N, 15.90. Found: C, 64.55; H, 5.48; N, 15.69.

1,2,3,4,7,8,9,10-Octahydro-2H,6H-pyrimido[1,2-$a$]thiopyrano[4',3':4,5]thieno[2,3-$d$]-pyrimidin-6-one (4e). From ethyl 2-amino-4,7-dihydro-5$H$-thieno[2,3-$c$]thiopyran-3-carboxylate; $^{20}$ in HMPA at 150 °C; 3 h. Yield 2.26 g colorless crystals, 81%; mp >320 °C; $^1$H NMR (DMSO-$d_6$): δ 7.80 (s, 1H), 3.85 (m, 2H), 3.73 (s, 2H), 3.25 (m, 2H), 3.05 (m, 2H), 2.90 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C$_{12}$H$_{13}$N$_3$O$_2$ (279.37): C, 51.59; H, 4.69; N, 15.04. Found: C, 51.32; H, 4.45; N, 14.82.

1,2,3,4,7,8,9,10-Octahydro-2H,6H-pyrano[4,5-$d$]pyrimidin-6-imine (5a). From 2-amino-5,6-dihydro-4$H$-cyclopenta[$b$]thiophene-3-carbonitrile; $^{21}$ in HMPA at 150 °C; 2 h. Yield 1.50 g red crystals, 61%; mp 310 °C; $^1$H NMR (DMSO-$d_6$): δ 7.50 (s, 1H), 6.50 (s, 1H), 3.90 (m, 2H), 3.20 (m, 2H), 2.90 (m, 2H), 2.70 (m, 2H), 2.40 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C$_{12}$H$_{14}$N$_4$S (246.33): C, 58.51; H, 5.73; N, 22.74. Found: C, 58.29; H, 5.65; N, 22.52.

1,2,3,4,7,8,9,10-Octahydro-2H,6H-[1]benzothieno[2,3-$d$]pyrimido[1,2-$a$]pyrimidin-6-imine (5b). From 2-amino-4,5,6,7-tetrahydrobenzo-$b$thiophene-3-carbonitrile; $^{17}$ in HMPA at 150 °C; 2 h. Yield 1.75 g pale brown crystals, 67%; mp 277 °C; $^1$H NMR (DMSO-$d_6$): δ 7.40 (s, 1H), 6.70 (s, 1H), 3.90 (m, 2H), 3.20 (m, 2H), 2.70 (m, 2H), 1.90 (m, 2H), 1.70 (m, 4H). Anal. Calcd. for C$_{13}$H$_{16}$N$_4$S (260.36): C, 59.97; H, 6.20; N, 21.52. Found: C, 59.73; H, 6.20; N, 21.21.
**1,2,3,4,7,8,9,10-Octahydro-6H-cyclohepta[b]thiophene-3-carbonitrile**;\(^{22}\) in HMPA at 150 °C; 1 h. Yield 1.79 g pale brown crystals, 65%; mp 248 °C; \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 7.40 (s, 1H), 6.70 (s, 1H), 3.80 (m, 2H), 3.20 (m, 2H), 3.10 (m, 2H), 2.60 (m, 2H), 1.90 (m, 2H), 1.80 (m, 2H), 1.60 (m, 4H). Anal. Calcd. for C\(_{14}\)H\(_{18}\)N\(_4\)S (274.38): C, 61.28; H, 6.61; N, 20.42. Found: C, 61.01; H, 6.33; N, 20.22.

**1,2,3,4,6,7,8,9-Octahydro-(phenylmethyl)-6H-pyrido[4',3':4,5]thieno[2,3-d]pyrimido[1,2-a]pyrimidin-6-imine** (5d). From 2-amino-4,5,6,7-tetrahydro-6-(phenylmethyl)thieno[2,3-c]pyridine-3-carbonitrile;\(^{23}\) in HMPA at 150 °C; 3 h. Yield 2.53 g pale brown crystals, 72%; mp 261 °C; \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 7.40 (s, 1H), 7.30 (m, 5H), 6.60 (s, 1H), 3.90 (m, 2H), 3.60 (s, 2H), 3.50 (s, 2H), 3.20 (m, 2H), 2.90 (m, 2H), 2.70 (m, 2H), 1.90 (m, 2H). Anal. Calcd. for C\(_{19}\)H\(_{21}\)N\(_5\)S (351.47): C, 64.93; H, 6.02; N, 19.93. Found: C, 64.62; H, 5.80; N, 19.67.

**1,2,3,4,7,8,9,10-Octahydro-9-methyl-6H-pyridino[1,2-a]benzothieno[2,3-d]pyrimido[1,2-a]pyrimidin-6-imine** (5f). From 2-amino-4,5,6,7-tetrahydro-6-methylbenzo[b]thiophene-3-carbonitrile;\(^{22}\) in HMPA at 150 °C; 2 h. Yield 2.0 g yellow crystals, 73%; mp 274 °C; \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 7.60 (s, 1H), 6.60 (s, 1H), 3.80 (m, 2H), 3.20 (m, 2H), 2.90–1.20 (m, 9H), 1.10 (d, 3H, J=7.1Hz). Anal. Calcd. for C\(_{14}\)H\(_{18}\)N\(_4\)S (274.38): C, 61.28; H, 6.61; N, 20.42. Found: C, 60.97; H, 6.40; N, 20.22.

**1,2,3,4,7,8,9,10-Octahydro-9-methyl-6H-pyrido[4',3':4,5]thieno[2,3-d]pyrimido[1,2-a]pyrimidin-6-imine** (5g). From 2-amino-4,5,6,7-tetrahydro-6-methylthieno[2,3-c]pyridine-3-carbonitrile;\(^{24}\) in HMPA at 150 °C; 3 h. Yield 1.87 g yellow crystals, 68%; mp 288 °C; \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 7.60 (s, 1H), 6.70 (s, 1H), 3.90 (m, 2H), 3.40 (s, 2H), 3.20 (m, 2H), 2.80 (m, 2H), 2.60 (m, 2H), 2.30 (m, 3H), 1.90 (m, 2H). Anal. Calcd. for C\(_{13}\)H\(_{17}\)N\(_5\)S (275.37): C, 56.70; H, 6.22; N, 25.43. Found: C, 56.62; H, 6.12; N, 25.24.

**1,2,3,4,7,8,9,10-Octahydro-6H-benzofuro[2,3-d]pyrimido[1,2-a]pyrimidin-6-imine** (5h). From 2-amino-4,5,6,7-tetrahydrobenzofuran-3-carbonitrile;\(^{25}\) in HMPA at 150 °C; 1 h. Yield 1.52 g colorless crystals, 62%; mp 290 °C; \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 7.50 (s, 1H), 6.30 (s, 1H), 3.80 (m, 2H), 3.20 (m, 2H), 2.50 (m, 4H), 1.90 (m, 2H), 1.70 (m,
4H). Anal. Calcd. for C$_{13}$H$_{16}$N$_{4}$O (244.30): C, 63.92; H, 6.60; N, 22.93. Found: C, 63.78; H, 6.65; N, 22.64.

References

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