Reagents for new heteroannelation reactions part V: 2-(methylthio)-2-imidazoline

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Abstract
Double annelation of an imidazo[1,2-a]pyrimidine moiety was achieved in a one-pot process by reacting heteroaromatic 2-aminoesters and 2-aminonitriles with 2-(methylthio)-2-imidazoline, obtaining a number of mostly novel tetracyclic hetero-systems.

Keywords: Methylthioimidazoline, aminoesters, aminonitriles

Introduction
Within a long-term project dealing with the synthesis of novel fused heterocyclic systems we have shown that compounds of a N-[bis(methylthio)methylene]-amino (BMMA) type are versatile reagents for a one-pot annelation of a pyrimidine ring to 2-aminoesters:

Furthermore we have extended this methodology towards cyclic analogs of the BMMA reagents, using methylthio-substituted thiazole and thiazine derivatives for double-annelation reactions¹:
In the present paper we report on the utilization of 2-(methylthio)-2-imidazoline (1) for double annelation reactions, expanding the BMMA strategy towards the construction of \( \text{N,N-} \)heterocycles.

\[
\text{1} \quad n = 1, 2
\]

**Results and Discussion**

In contrast to the cyclizations of the thiazole and thiazine reagents, heating in dry acetic acid turned out to be unsuccessful in case of 1. Thus in a large number of experiments optimal conditions concerning solvent and temperature had to be revealed. Finally, heating the starting materials in HMPA at 160 °C for several hours proved to yield best results, and a variety of heteroaromatic substrates was reacted with 2-(methylthio)-2-imidazoline to obtain the desired tetracyclic fusion products:
Annelation of 1 with 2-aminoesters produced oxo compounds 2,

\[
\text{Compd} \quad X
\]
\[
\begin{array}{ccc}
2a & \text{CH-CH}_3 \\
2b & \text{N-CH}_2\text{-Ph} \\
2c & S
\end{array}
\]

whereas 2-aminonitriles gave the analogous imino derivatives 3 and 4.

\[
\text{Compd} \quad X \quad Y \quad n
\]
\[
\begin{array}{cccc}
3a & \text{CH}_2 & \text{S} & 1 \\
3b & \text{CH}_2 & \text{S} & 2 \\
3c & \text{CH-CH}_3 & \text{S} & 2 \\
3d & \text{CH}_2 & \text{S} & 3 \\
3e & \text{N-CH}_3 & \text{S} & 2 \\
3f & \text{N-CH}_2\text{-Ph} & \text{S} & 2 \\
3g & \text{S} & \text{S} & 2 \\
4 & \text{CH}_2 & \text{O} & 2
\end{array}
\]

Some compounds derived from parent systems described here have already been synthesized by alternative, multi-step pathways. However, the method reported here allows smooth access to complex fused products starting from easily obtainable substrates (e.g. by Gewald reaction) in one step.
Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. \(^1\)H and \(^13\)C NMR spectra were recorded on a Bruker AC 200 spectrometer (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-(Methylthio)-2-imidazoline (1) was prepared via a two step procedure from ethylene diamine, CS\(_2\), and methyl iodide. The starting aminoesters and aminonitriles were prepared according to literature procedures.

General procedure for the reaction of 1 with 2-aminoesters. Synthesis of compounds 2a-c

2-(Methylthio)-2-imidazoline (3 mmol) and the aminoester (2 mmol) were dissolved in hexamethylphosphoric acid triamide (3 mL) and heated to 160 °C for 3 h. After cooling to room temperature, crushed ice was added and the mixture stirred for 1 h. The separated product was collected by filtration and crystallized from an appropriate solvent.

2,3,6,7,8,9-Hexahydro-8-methyl-[1]benzothieno[2,3-d]imidazo[1,2-a]pyrimidin-5(1H)-one (2a)

From ethyl 2-amino-4,5,6,7-tetrahydro-6-methylbenzo[b]thiophene-3-carboxylate; yield: 76%; m.p.: 290 °C (methanol); \(C_{13}H_{15}N_3OS\) (261.34); \(^1\)H-NMR \(\delta\) 7.70 (s, 1H), 4.00 (t, 2H), 3.60 (t, 2H), 2.90-1.20 (m, 7H), 1.00 (d, 3H); \(^13\)C-NMR \(\delta\) 166.00 (s), 156.95 (s), 155.43 (s), 129.50 (s), 124.81 (s), 113.82 (s), 41.81 (2t), 32.37 (t), 30.16 (t), 28.90 (d), 24.82 (t), 21.18 (q).

2,3,6,7,8,9-Hexahydro-8-(phenylmethyl)-imidazo[1,2-a]pyrido[4´,3´:4,5]thieno-[2,3-d]pyrimidin-5(1H)-one (2b)

From ethyl 2-amino-4,5,6,7-tetrahydro-6-(phenylmethyl)thieno[2,3-c]pyridine-3-carboxylate; yield: 73%; m.p.: 235 °C (acetone); \(C_{18}H_{18}N_4OS\) (338.43); calc.: C 63.88%, H 5.36%, N 16.55%; found: C 63.67%, H 5.23%, N 16.56%; \(^1\)H-NMR: \(\delta\) 7.70 (s, 1H), 7.40-7.20 (m, 5H), 4.00 (s, 2H), 4.00 (s, 2H), 3.60 (s, 2H), 3.50 (s, 2H), 2.80-2.60 (m, 4H).

1,2,3,6,7,9-Hexahydro-5H-imidazo[1,2-a]thiopyrano[4´,3´:4,5]thieno[2,3-d]pyrimidin-5-one (2c)

From ethyl 2-amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-carboxylate; yield: 73%; m.p.: 245 °C (methanol); \(C_{11}H_{11}N_3OS_2\) (265.36); calc.: C 49.78%, H 4.18%, N 15.84%; found: C 49.38%, H 4.04%, N 16.01%; \(^1\)H-NMR: \(\delta\) 7.90 (s, 1H), 4.00 (t, 2H), 3.80 (s, 2H), 3.60 (t, 2H), 3.00 (s, 2H), 2.80 (s, 2H); \(^13\)C-NMR: \(\delta\) 165.25 (s), 156.78 (s), 155.87 (s), 129.69 (s), 121.20 (s), 113.90 (s), 41.98 (t), 41.98 (t), 27.17 (t), 24.68 (t), 24.24 (t).

General procedure for the reaction of 1 with 2-aminonitriles

Synthesis of compounds 3a-g and 4 2-Methylthio-2-imidazoline (5 mmol) and the aminonitrile (3 mmol) were dissolved in hexamethylphosphonic acid triamide (3 mL) and heated to 160 °C for
a given period of time. After cooling to room temperature, crushed ice was added and the mixture stirred for 1 h. The separated product was collected by filtration and crystallized from an appropriate solvent.

**1,2,3,6,7,8-Hexahydro-5H-cyclopenta[4,5]thieno[2,3-d]imidazo[1,2-a]pyrimidin-5-imine (3a).** From 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile; reaction time: 3 h; yield: 56%; m.p.: >320 °C (methanol); C₁₁H₁₂N₄S (232.30); ¹H-NMR: δ 7.50 (s, 1H), 6.50 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 2.90 (t, 2H), 2.80 (t, 2H), 2.30 (m, 2H); ¹³C-NMR: δ 166.45 (s), 155.79 (s), 154.97 (s), 137.90 (s), 129.82 (s), 109.40 (s), 42.84 (t), 42.84 (t), 28.68 (t), 28.58 (t), 27.32 (t).

**2,3,6,7,8,9-Hexahydro-[1]benzothieno[2,3-d]imidazo[1,2-a]pyrimidin-5(1H)-imine (3b).** From 2-amino-4,5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile; reaction time: 3 h; yield: 56%; m.p.: >320 °C (methanol); C₁₁H₁₂N₄S (232.30); ¹H-NMR: δ 7.50 (s, 1H), 6.50 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 2.90 (t, 2H), 2.80 (t, 2H), 2.30 (m, 2H); ¹³C-NMR: δ 166.45 (s), 155.79 (s), 154.97 (s), 137.90 (s), 129.82 (s), 109.40 (s), 42.84 (t), 42.84 (t), 28.68 (t), 28.58 (t), 27.32 (t).

**2,3,6,7,8,9-Hexahydro-8-methyl-[1]benzothieno[2,3-d]imidazo[1,2-a]pyrimidin-5(1H)-imine (3c).** From 2-amino-4,5,6-tetrahydro-6-methylbenzothiophene-3-carbonitrile; reaction time: 4 h; yield: 59%; m.p.: 265 °C (methanol); C₁₂H₁₄N₄S (246.33); ¹H-NMR: δ 7.40 (s, 1H), 6.60 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 2.50 (t, 2H), 1.80 (m, 4H); ¹³C-NMR: δ 160.44 (s), 155.02 (s), 152.43 (s), 129.37 (s), 124.60 (s), 111.96 (s), 42.54 (t), 39.65 (t), 25.61 (t), 24.34 (t), 22.39 (t), 22.08 (t).

**2,3,6,7,8,9-Hexahydro-8-methylimidazo[1,2-a]pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-5(1H)-imine (3e).** From 2-amino-4,5,6,7-tetrahydro-6-methylbenzothiophene-3-carbonitrile; reaction time: 3 h; yield: 46%; m.p.: 262 °C (ethyl acetate); C₁₂H₁₅N₅S (261.34); ¹H-NMR: δ 7.50 (s, 1H), 6.40 (s, 1H), 3.90 (t, 2H), 3.50 (t, 2H), 3.20 (m, 2H), 2.70 (m, 2H), 1.80 (m, 2H), 1.60 (m, 4H); ¹³C-NMR: δ 158.71 (s), 154.63 (s), 151.35 (s), 135.82 (s), 128.19 (s), 113.47 (s), 48.55 (t), 42.25 (t), 31.68 (t), 28.58 (t), 27.80 (t), 27.54 (t), 26.74 (t).
2,3,6,7,8,9-Hexahydro-8-(phenylmethyl)-imidazo[1,2-a]pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-5(1H)-imine (3f). From 2-amino-4,5,6,7-tetrahydro-6-(phenylmethyl)-thieno[2,3-c]pyridine-3-carbonitrile; reaction time: 3 h; yield: 53%; m.p.: 205 °C (ethyl acetate); C_{18}H_{19}N_{5}S (337.44); ^{1}H-NMR: 7.50 (s, 1H), 7.40-7.20 (m, 5H), 6.40 (s, 1H), 3.90 (t, 2H), 3.70 (s, 2H), 3.60 (t, 2H), 3.40 (s, 2H), 2.80 (t, 2H); ^{13}C-NMR: δ 161.05 (s), 155.15 (s), 152.15 (s), 138.22 (s), 128.74 (2d), 128.20 (2d), 127.93 (s), 126.99 (s), 122.22 (s), 111.62 (s), 60.89 (t), 51.10 (t), 42.53 (2t), 25.94 (t).

1,2,3,6,7,9-Hexahydro-5H-imidazo[1,2-a]thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-5-imine (3g). From 2-amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-carbonitrile; reaction time: 12 h; yield: 56%; m.p.: >320 °C (methanol); C_{11}H_{12}N_{4}S_{2} (264.36); ^{1}H-NMR: δ 7.50 (s, 1H), 6.50 (s, 1H), 3.90 (t, 2H), 3.70 (t, 2H), 3.60 (t, 2H), 3.10 (m, 2H), 2.90 (m, 2H); ^{13}C-NMR: δ 160.21 (s), 155.10 (s), 151.56 (s), 129.51 (s), 120.79 (s), 112.21 (s), 42.54 (2t), 27.72 (t), 25.02 (t), 24.65 (t).

2,3,6,7,8,9-Hexahydrobenzofuro[2,3-d]imidazo[1,2-a]pyrimidin-5(1H)-imine (4). From 2-amino-4,5,6,7-tetrahydrobenzofuran-3-carbonitrile; reaction time: 3 h; yield: 58%; m.p.: 278 °C (methanol); C_{12}H_{14}N_{4}O (230.27); ^{1}H-NMR: δ 7.60 (s, 1H), 6.20 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 2.70-2.50 (m, 4H), 1.80-1.60 (m, 4H); ^{13}C-NMR: δ 162.81 (s), 156.71 (s), 153.55 (s), 144.53 (s), 113.78 (s), 95.64 (s), 49.06 (t), 42.98 (t), 22.73 (t), 22.65 (t), 21.37 (t).

References