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

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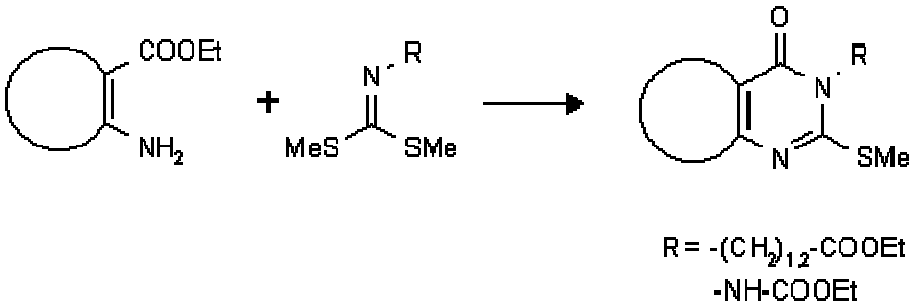
Abstract

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.

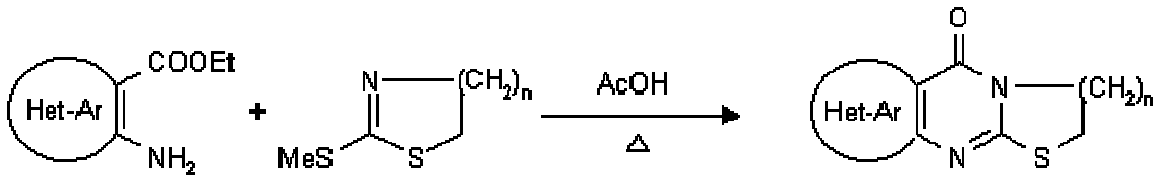
Keywords: Methylthioimidazoline, aminoesters, aminonitriles

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:

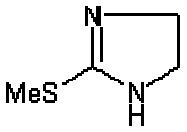


Furthermore we have extended this methodology towards cyclic analogs of the BMMA reagents, using methylthio-substituted thiazole and thiazine derivatives for double-annelation reactions[1]:



n = 1,2

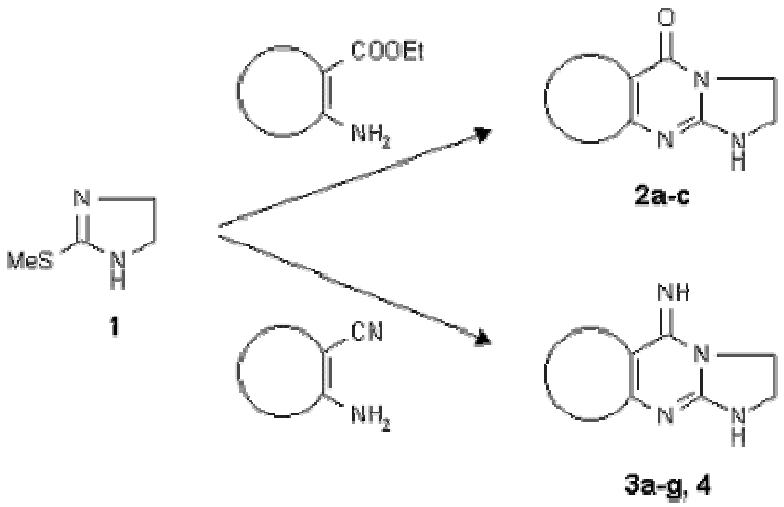
In the present paper we report on the utilization of 2-(methylthio)-2-imidazoline (1) for double annelation reactions, expanding the BMMA strategy towards the construction of N,N-heterocycles.



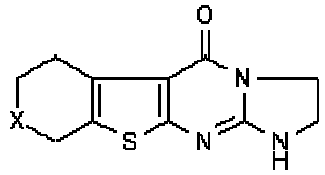
1

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 ^{o}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:



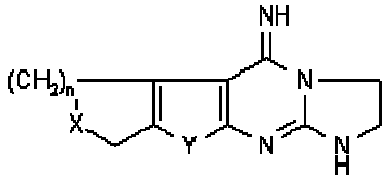
Annelation of 1 with 2-aminoesters produced oxo compounds 2,



2

Compd	X
2a	CH-CH_3
2b	N-CH_2-Ph
2c	S

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



3, 4

Compd	X	Y	n
3a	CH_2	S	1
3b	CH_2	S	2
3c	CH-CH_3	S	2
3d	CH_2	S	3
3e	N-CH_3	S	2
3f	N-CH_2-Ph	S	2
3g	S	S	2
4	CH_2	O	2

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, δ-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 ^{o}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 ^{o}C (methanol); $C_{13}H_{15}N_3OS$ (261.34); ^{1}H-NMR δ 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 δ 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(1*H*)-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 ^{o}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: δ 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-5*H*-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 ^{o}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: δ 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: δ 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 hexamethylphosphoric acid triamide (3 mL) and heated to 160 ^{o}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-5*H*-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 ^{o}C (methanol); $C_{11}H_{12}N_4S$ (232.30); ^{1}H-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); ^{13}C-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(1*H*)-imine (3b). From 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile; reaction time: 10 h; yield: 61%; m.p.: 265 ^{o}C (methanol); $C_{12}H_{14}N_4S$ (246.33); ^{1}H-NMR: δ 7.40 (s, 1H), 6.60 (s, 1H), 3.90 (t, 2H), 3.80 (t, 2H), 3.60 (t, 2H), 2.50 (t, 2H), 1.80 (m, 4H); ^{13}C-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-methyl-[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidin-5(1*H*)-imine (3c). From 2-amino-4,5,6,7-tetrahydro-6-methylbenzo[b]thiophene-3-carbonitrile; reaction time: 4 h; yield: 59%; m.p.: 266 ^{o}C (methanol); $C_{13}H_{16}N_4S$ (260.36); ^{1}H-NMR: δ 7.40 (s, 1H), 6.50 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 2.70 (m, 2H), 2.20 (m, 2H), 1.80 (m, 2H), 1.20 (m, 1H), 1.00 (d, 3H).

1,2,3,6,7,8,9,10-Octahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]imidazo[1,2-*a*]pyrimidin-5-imine (3d). From 2-amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile[11]; reaction time: 3 h; yield: 57%; m.p.: 237 ^{o}C (methanol); $C_{13}H_{16}N_4S$ (260.36); ^{1}H-NMR: δ 7.40 (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); ^{13}C-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-methylimidazo[1,2-*a*]pyrido[4´,3´:4,5]thieno[2,3-*d*]pyrimidin-5(1*H*)-imine (3e). From 2-amino-4,5,6,7-tetrahydro-6-methylthieno[2,3-c]pyridine-3-carbonitrile; reaction time: 3 h; yield: 46%; m.p.: 262 ^{o}C (ethyl acetate); $C_{12}H_{15}N_5S$ (261.34); ^{1}H-NMR: δ 7.50 (s, 1H), 6.40 (s, 1H), 3.90 (t, 2H), 3.60 (t, 2H), 3.40 (s, 2H), 2.90 (t, 2H), 2.60 (t, 2H), 2.30 (s, 3H); ^{13}C-NMR: δ 160.90 (s), 155.20 (s), 152.20 (s), 127.67 (s), 122.21 (s), 111.71 (s), 53.09 (t), 51.01 (t), 45.06 (t), 42.51 (t), 39.71 (t), 26.09 (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(1*H*)-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 ^{o}C (ethyl acetate); $C_{18}H_{19}N_5S$ (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), 2.70 (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), 49.19 (t), 42.53 (2t), 25.94 (t).

1,2,3,6,7,9-Hexahydro-5*H*-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[13]; reaction time: 12 h; yield: 56%; m.p.: >320 ^{o}C (methanol); $C_{11}H_{12}N_4S_2$ (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(1*H*)-imine (4). From 2-amino-4,5,6,7-tetrahydrobenzofuran-3-carbonitrile; reaction time: 3 h; yield: 58%; m.p.: 278 ^{o}C (methanol); $C_{12}H_{14}N_4O$ (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), 22.56 (t), 21.37 (t).

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