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Reagents for New Heteroannelation Reactions III [1]. 2-(Methylthio)-2-thiazoline◇

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Summary. A variety of partly novel tri- and tetracyclic hetero systems were obtained by reaction of heteroaromatic 2-aminoesters with 2-(methylthio)-2-thiazoline, yielding double-annelation of a thiazolo[2,3-*b*]pyrimido moiety in a one-pot process.

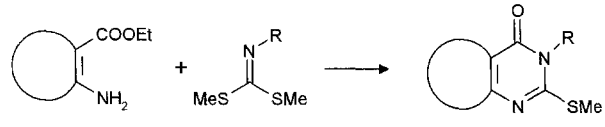
Keywords. Fused S,N-heterocycles; Fused thieno[2,3-*d*]pyrimidines; 2-(Methylthio)-2-thiazoline.

Reagentien für neue Heteroanellierungsreaktionen, 3. Mitt. [1]. **2-(Methylthio)-2-thiazolin**

Zusammenfassung. Eine Reihe z.T. neuer tri- und tetracyclischer Heterosysteme wurde durch Reaktion von heteroaromatischen 2-Aminoestern mit 2-(Methylthio)-2-thiazolin erhalten, wobei im Eintopfverfahren durch doppelte Cyclisierung jeweils eine Thiazolo[2,3-*b*]pyrimido-Einheit anelliert wurde.

Introduction

Within a long-term project dealing with novel fused and spiro-substituted heterocyclic systems, we reported in earlier papers [2, 3] on heteroannelations to fused pyrimidines, achieved by reacting 2-aminoesters or (in many cases) 2-aminonitriles with new reagents belonging to a N-(*bis*(methylthio)methylene)-amino (*BMMA*) type.



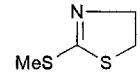
R = -$(CH_2)_{1,2}$-COOEt
-NH-COOEt

In one of these papers [2], we also mentioned a trial reaction with ethyl 2-(methylthio)-2-thiazoline-4-carboxylate as our first example for the use of *cyclic*

◇ Dedicated to pharmacist *T. Mayrhofer*, the long-standing sponsor of pharmaceutical research, on the occasion of his 90th birthday

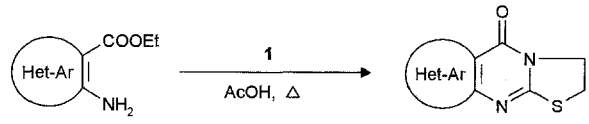
On leave from University of Chittagong, Bangladesh

BMMA reagents. As this test yielded an acceptable result (57%), it was fair to assume that 2-(methylthio)-2-thiazoline (**1**) might also give the desired cyclizations with various 2-aminoesters containing groups of sufficient nucleophilicity.



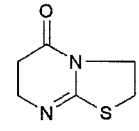
1

The present paper extends our BMMA method to the readily available **1** [4, 5], studying its applicability to a variety of heteroaromatic substrates.



Results and Discussion

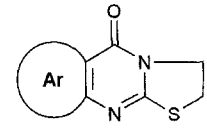
Whereas open-chain aminoesters gave only poor results (*e.g.* β-alanine: 23% of **2**),



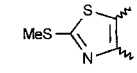
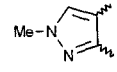
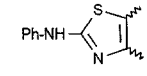
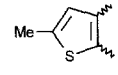
2

a series of heteroaromatic 2-aminoesters (*e.g.* various products of *Gewald* reactions) reacted readily with **1** to give

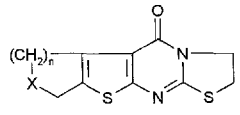
(*i*) the desired tricyclic fusion products **3**



3

Compd	Ar	Compd	Ar
3a		**3e**	
3b		**3f**	
3c		**3g**	
3d			

(*ii*) and the tetracyclic fusion products **4**.



4

Compd	X	n
4a	CH_2	2
4b	S	2
4c	Ph-CH_2-N	2
4d	Me-CH	2
4e	CH_2	3
4f	CH_2	1

It should be pointed out that some of the products thus obtained are either identical or at least derived from parent systems already obtained many years ago by alternative, multi-step pathways [6–9].

Various solvents and different reaction conditions were applied to accomplish the desired cyclizations. Most of them (*e.g. HMPA*/160°C, diglyme/160°C, benzene/80°C, trichlorobenzene/180°C, EtOH + TsOH/80° C, $CHCl_3$/reflux, dry acetone + TsOH/reflux) gave no reaction at all. Crude acetic acid/100°C yielded acetylated products, whereas positive results were obtained in dry acetic acid at 100°C, giving yields of *ca.* 60–66% (not yet optimized).

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer (*TMS* as internal standard, $CDCl_3$ or *DMSO*-d_6 as solvent, δ in ppm). Elementary analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. *J. Theiner*).

2-(Methylthio)-2-thiazoline was prepared *via* a two-step procedure from 2-aminoethanol, CS_2, and methyl iodide [4, 5]. Ethyl 3-aminopropanoate and methyl 2-aminobenzoate were purchased from Aldrich; all other aminoesters were prepared according to literature procedures. For compounds **3a** [10], **3c** [11], **4a** [6, 9], and **4b** [12] (which were already known, but synthesized by other methods), physical properties are in agreement with published data.

General procedure for the cyclization reaction

Equimolar amounts of 2-(methylthio)-2-thiazoline and aminoester were heated to 100°C in dry acetic acid for an appropriate 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 crystallized from ethanol or methanol.

2,3,6,7-Tetrahydro-5H-thiazolo[3,2-a]pyrimidin-5-one (**2**)

From ethyl 3-aminopropanoate; reaction time: 16 h; yield: 23%; m.p.: 222–223°C; $C_6H_8N_2OS$ (156.20); ^1H NMR (*DMSO*-d_6): 3.90 (t, 2H), 3.30 (t, 2H), 2.80 (t, 2H), 2.60 (t, 2H); ^{13}C NMR (*DMSO*-d_6): 169.88 (s), 153.61 (s), 41.93 (t), 35.74 (t), 34.20 (t), 31.01 (t).

2,3-Dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (**3a**)

From methyl 2-aminobenzoate; reaction time: 9 h; yield: 68%; m.p.: 158° C; $C_{10}H_8N_2OS$ (204.25); ^1H NMR ($CDCl_3$): 8.10 (d, 1H), 7.70–7.20 (m, 3H) 4.50 (t, 2H), 3.50 (t, 2H); ^{13}C NMR ($CDCl_3$):

159.89 (s), 159.15 (s), 148.38 (s), 134.07 (s), 125.96 (d), 125.52 (d), 125.40 (d), 118.46 (d), 47.95 (t), 26.02 (t).

6,7-Dihydropyrazolo[3,4-d]thiazolo[3,2-a]pyrimidin-4(1H)-one (**3b**)

From ethyl 5-amino-1H-pyrazole-4-carboxylate [13]; reaction time: 5 h; yield: 62%; m.p.: 300°C; $C_7H_6N_4OS$ (194.21); calc.: C 43.29%, H 3.11%, N 28.84%; found: C 43.59%, H 2.86%, N 28.81%; ^{1}H NMR (*DMSO*-d_6): 13.50 (s, 1H), 8.10 (s, 1H), 4.30 (t, 2H), 3.50 (t, 2H); ^{13}C NMR (*DMSO*-d_6): 163.31 (s), 156.19 (s), 155.20 (s), 133.48 (d), 102.42 (s), 47.84 (t), 26.64 (t).

6,7-Dihydro-2-methylpyrazolo[3,4-d]thiazolo[3,2-a]pyrimidin-4(2H)-one (**3c**)

From ethyl 3-amino-1-methyl-1*H*-pyrazole-4-carboxylate [14]; reaction time: 5 h; yield: 60%; m.p.: 292–293°C; $C_8H_8N_4OS$ (208.24); ^{1}H NMR (*DMSO*-d_6): 8.50 (s, 1H), 4.30 (t, 2H), 3.90 (s, 3H), 3.90 (t, 2H); ^{13}C NMR (*DMSO*-d_6): 161.81 (s), 159.10 (s), 156.68 (s), 129.55 (d), 103.63 (s), 47.58 (t), 39.77 (q), 26.07 (t).

2,3-Dihydro-7-methyl-5H-thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one (**3d**)

From ethyl 2-amino-5-methylthiophene-3-carboxylate [15]; reaction time: 4 h; yield: 68%; m.p.: 160°C; $C_9H_8N_2OS_2$ (224.30); ^{1}H NMR ($CDCl_3$): 6.90 (s, 1H), 4.50 (t, 2H), 3.40 (t, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): 163.59 (s), 158.89 (s), 156.18 (s), 136.07 (s), 120.47 (s), 118.32 (d), 48.02 (t), 26.74 (t), 15.63 (q).

6,7-Dihydro-9H-thiazolo[3,2-a]thieno[3,2-d]pyrimidin-9-one (**3e**)

From ethyl 3-aminothiophene-2-carboxylate [16]; reaction time: 4 h; yield: 65%; m.p.: 288°C; $C_8H_6N_2OS_2$ (210.27); ^{1}H NMR ($CDCl_3$): 7.70 (d, 1H), 7.10 (d, 1H), 4.50 (t, 2H), 3.50 (t, 2H); ^{13}C NMR ($CDCl_3$): 161.46 (s), 157.80 (s), 156.56 (s), 134.34 (d), 124.01 (d), 119.21 (s), 48.22 (t), 26.89 (t).

6,7-Dihydro-2-(methylthio)-9H-dithiazolo[3,2-a:4,5-d]pyrimidin-9-one (**3f**)

From ethyl 4-amino-2-(methylthio)-thiazole-5-carboxylate [17]; reaction time: 10 h; yield: 64%; m.p.: 178°C; $C_8H_7N_3OS_3$ (257.34); ^{1}H NMR ($CDCl_3$): 4.50 (t, 2H), 3.50 (t, 2H), 2.70 (s, 3H); ^{13}C MNR ($CDCl_3$): 176.72 (s), 166.48 (s), 163.89 (s), 155.52 (s), 111.82 (s), 48.49 (t), 26.80 (t), 16.10 (q).

6,7-Dihydro-2-(phenylamino)-9H-dithiazolo[3,2-a:4,5-d]pyrimidin-9-one (**3g**)

From ethyl 4-amino-2-(phenylamino)-thiazole-5-carboxylate [18]; reaction time: 12 h; yield: 61%; $C_{13}H_{10}N_4OS_2$ (302.37); calc.: C 51.63%, H 3.33%, N 18.52%; found C 51.46%, H 3.17%, N 18.38%; ^{1}H NMR (*DMSO*-d_6): 11.00 (s, 1H), 7.70 (d, 2H), 7.40 (m, 2H), 7.10 (m, 1H), 4.40 (t, 2H), 3.60 (t, 2H); ^{13}C NMR (*DMSO*-d_6): 166.72 (s), 165.98 (s), 163.66 (s), 155.22 (s), 139.56 (s), 129.03 (2d), 123.11 (d), 118.39 (2d), 102.97 (s), 48.61 (t), 26.52 (t).

2,3,6,7,8,9-Hexahydro-5H-[1]benzothieno[2,3-d]thiazolo[3,2-a]pyrimidin-5-one (**4a**)

From ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate [19]; reaction time: 5 h; yield: 66%; m.p.: 226–227°C; $C_{12}H_{12}N_2OS_2$ (264.36); ^{1}H NMR (*DMSO*-d_6): 4.35 (t, 2H), 3.60 (t,

2H), 2.80 (m, 2H), 2.70 (m, 2H), 1.80 (m, 4H); ^{13}C NMR (*DMSO*-d_6): 162.00 (s), 160.00 (s), 156.39 (s), 130.74 (s), 130.34 (s), 118.08 (s), 48.18 (t), 26.72 (t), 25.13 (t), 24.36 (t), 22.45 (t), 21.71 (t).

2,3,6,9-Tetrahydro-5H,7H-thiazolo[3,2-a]thiopyrano[4',3':4,5]-thieno[2,3-d]pyrimidin-5-one (**4b**)

From ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-c]thiopyran-3-carboxylate [20]; reaction time: 5 h; yield: 63%; m.p.: 207–209°C; $C_{11}H_{10}N_2OS_3$ (282.39); ^{1}H NMR ($CDCl_3$): 4.30 (t, 2H), 3.60 (s, 2H), 3.40 (t, 2H), 3.10 (t, 2H), 2.80 (t, 2H); ^{13}C NMR ($CDCl_3$): 162.83 (s), 159.65 (s), 157.01 (s), 130.55 (s), 127.44 (s), 118.78 (s), 48.04 (t), 27.18 (t), 26.86 (t), 25.42 (t), 25.30 (t).

2,3,6,7,8,9-Hexahydro-8-(phenylmethyl)-5H-pyrido[4',3':4,5]thieno[2,3-d]-thiazolo[3,2-a]pyrimidin-5-one (**4c**)

From ethyl 2-amino-4,5,6,7-tetrahydro-6-(phenylmethyl)-thieno[2,3-*c*]pyridine-3-carboxylate [21]; reaction time: 20 h; the product was purified by column chromatography (SiO_2, chloroform:acetone = 9:2); yield: 43%; m.p.: 138°C; $C_{18}H_{17}N_3OS_2$ (355.47); ^{1}H NMR ($CDCl_3$): 7.40 (m, 5H), 4.40 (t, 2H), 3.80 (s, 2H), 3.70 (s, 2H), 3.60 (t, 2H), 3.00-2.80 (m, 4H); ^{13}C NMR ($CDCl_3$): 163.19 (s), 160.47 (s), 156.17 (s), 136.55 (s), 129.18 (2d), 128.52 (2d), 128.29 (d), 127.44 (s), 127.16 (s), 117.94 (s), 60.34 (t), 50.38 (t), 48.74 (t), 48.12 (t), 26.77 (t), 24.88 (t).

2,3,6,7,8,9-Hexahydro-8-methyl-5H-[1]benzothieno[2,3-d]thiazolo[3,2-a]-pyrimidin-5-one (**4d**)

From ethyl 2-amino-4,5,6,7-tetrahydro-6-methylbenzo[*b*]thiophene-3-carboxylate [22]; reaction time: 5 h; yield: 59%; m.p.: 197–198°C; $C_{13}H_{14}N_2OS_2$ (278.38); ^{1}H NMR (*DMSO*-d_6): 4.35 (t, 2H), 3.60 (t, 2H), 2.90 (m, 2H), 2.80 (m, 2H), 2.40 (m, 1H), 1.90 (m, 2H), 1.50 (d, 3H); ^{13}C NMR (*DMSO*-d_6): 162.73 (s), 159.98 (s), 156.38 (s), 130.33 (s), 129.96 (s), 117.94 (s), 48.16 (t), 32.33 (t), 29.88 (t), 28.70 (d), 26.71 (t), 24.83 (t), 21.15 (q).

2,3,7,8,9,10-Hexahydro-5H,6H-cyclohepta[4,5]thieno[2,3-d]thiazolo[3,2-a]-pyrimidin-5-one (**4e**)

From ethyl 2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylate [23]; reaction time: 20 h at 60°C; yield: 61%; m.p.: 173–174°C; $C_{13}H_{14}N_2OS_2$ (278.38); ^{1}H NMR ($CDCl_3$): 4.50 (t, 2H), 3.50 (t, 2H), 3.30 (m, 2H), 2.80 (m, 2H), 2.00-1.60 (m, 6H); ^{13}C NMR ($CDCl_3$): 161.66 (s), 158.13 (s), 157.54 (s), 136.34 (s), 135.98 (s), 119.12 (s), 48.05 (t), 32.30 (t), 29.61 (t), 27.51 (2t), 27.00 (t), 26.79 (t).

2,3,7,8-Tetrahydro-5H,6H-cyclopenta[4,5]thieno[2,3-d]thiazolo[3,2-a]-pyrimidin-5-one (**4f**)

From ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate [19]; reaction time: 8 h; yield: 60%; m.p.: 203–204°C; $C_{11}H_{10}N_2OS_2$ (250.33); ^{1}H NMR ($CDCl_3$): 4.50 (t, 2H), 3.50 (t, 2H), 3.10–2.80 (m, 4H), 2.60–2.40 (m, 2H); ^{13}C NMR ($CDCl_3$): 168.38 (s), 158.36 (s), 156.85 (s), 139.44 (s), 137.08 (s), 116.12 (s), 48.00 (t), 29.33 (t), 28.71 (t), 27.68 (t), 26.92 (t).

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