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New Hetero-Annelation Reactions Using N-[*bis*-(Methylthio)-methylene]-amino and Related Reagents

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Summary. Reaction of acyclic ($\mathbf{R}_{1-3}$) and cyclic ($\mathbf{R}_{4-5}$) **BMMA** (=N-[*bis*-(**m**ethylthio)-**m**ethylene]-**a**mino) reagents with *Gewald*-type thiophene derivatives (**2**, **3**) led to annelation of pyrimidine moieties. Thus, linear thiazolo- or thiazino- and pyrrolo-, pyrido- or azepino-fused thiopyrano[4′,3′:4,5]thieno-[2,3-*d*]pyrimidines (**5** and **6**) as well as the angular imidazo-fused thiopyrano[4′,3′:4,5]thieno-[2,3-*d*]pyrimidine **8** were easily obtained from one-pot reactions in good yields.

Keywords. Fused S,N-heterocycles; *BMMA* reagents; Pyrimidine annelations.

Neue Heteroanellierungsreaktionen unter Verwendung von N-[*bis*-(Methylthio)-methylen]-amino und verwandten Reagenzien

Zusammenfassung. Umsetzung von acyclischen ($\mathbf{R}_{1-3}$) und cyclischen ($\mathbf{R}_{4-5}$) *BMMA*-Reagenzien (*BMMA* = N-[*bis*-(**M**ethylthio)-**m**ethylen]-**a**mino) mit *Gewald*-artigen Thiophenderivaten (**2**, **3**) führte zur Anellierung von Pyrimidinringen. Auf diese Weise konnten linear kondensierte Thiazolo- oder Thiazino- und Pyrrolo-, Pyrido- oder Azepinothiopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidine (**5** und **6**) sowie das angulär imidazo-anellierte Thiopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidin **8** in guten Ausbeuten auf direkte Weise in Eintopfreaktionen erhalten werden.

Introduction

We recently reported on the usefulness of *bis*-(methylthio)-methylene-amino (*BMMA*) reagents $\mathbf{R}_{1-3}$ (which also can be considered as dithioketals of isothiocyanates) for direct one-pot annelation of a (fused) pyrimidine moiety when starting from *ortho*-amino(hetero)aromatic esters, or of a pyrrolopyrimidine moiety when starting from *ortho*-amino(hetero)aromatic nitriles [1].

Even if known target systems were to be approached, this type of fusion reactions seems to be of some advantage as compared to known synthetic strategies – not only

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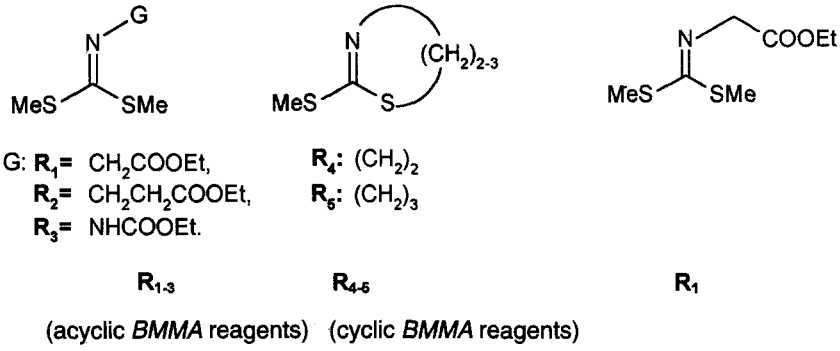
§ Dedicated with our very best wishes to our old friend and mentor *Hans Suschitzky*, em. Prof. at the University of Salford, GB, on the occasion of his 80th birthday; # on leave from Chemistry Department, Minia University, El-Minia, Egypt

by using readily accessible educts and reagents, but also by considerably abbreviating the route to the desired target systems.

This is even more true when derivatives of novel heterocyclic parent systems are aimed at. Among the various acyclic ($\mathbf{R}_{1-3}$) [2] and cyclic ($\mathbf{R}_{4-5}$) [2–3] *BMMA* reagents, the most straightforward one is $\mathbf{R}_1$ [4] (Scheme 1).



Scheme 1

In order to increase our knowledge about scope and limitations of this heteroannelation strategy, the present work [5] is dealing with its applications to amino ester (**2**) [6] and amino nitrile (**3**) [7] structures derived from the new thieno[2,3-*c*]-thiopyrane system, both of them readily accessible by *Gewald* reaction [8] from tetrahydrothiopyran-4-one (**1**) [9].

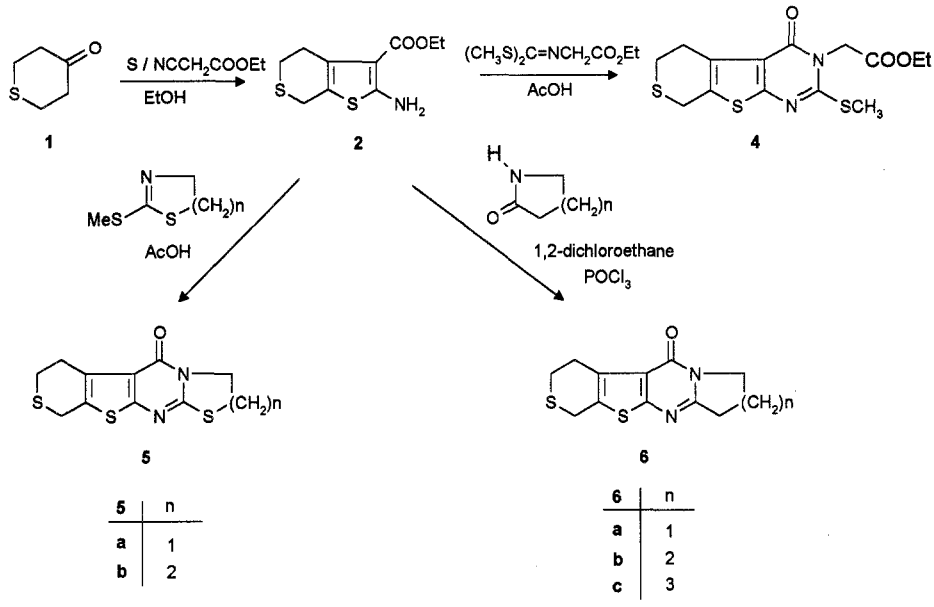
Results and Discussion

Use of the ester-type starting compound **2** (*cf.* Scheme 1) permitted the synthesis of the thiopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidine derivative **4** and to approach a variety of novel, structurally related linear and angular tetracyclic systems. The target systems were approached either by reacting **2** with the cyclic *BMMA* reagents $\mathbf{R}_4$ and $\mathbf{R}_5$ to yield **5a** and **5b** (which both are products of a one-pot double annelation at a thiazolopyrimido or a thiazinopyrimido moiety, respectively) or by reacting **2** with 5-, 6- and 7-membered lactams to obtain **6a–6c** (which both are products of a double annelation at a pyrrolopyrimido, a pyrido, a pyrimido, and an azepinopyrimido moiety, respectively).

The incorporation of lactams into our annelation studies was done with the intention to compare the results thus obtained with those reached by *BMMA* reagents and to access *via* these means the novel target compounds **6a–c** (Scheme 2).

Use of the nitrile-type starting compound **3** allowed a straightforward one-pot synthesis of **7–9**, *i.e.* of products derived from the novel tetracylic hetero-system imidazo[1,2-*c*]thiopyrano[4′,3′:4,5]thieno[3,2-*e*]pyrimidine.

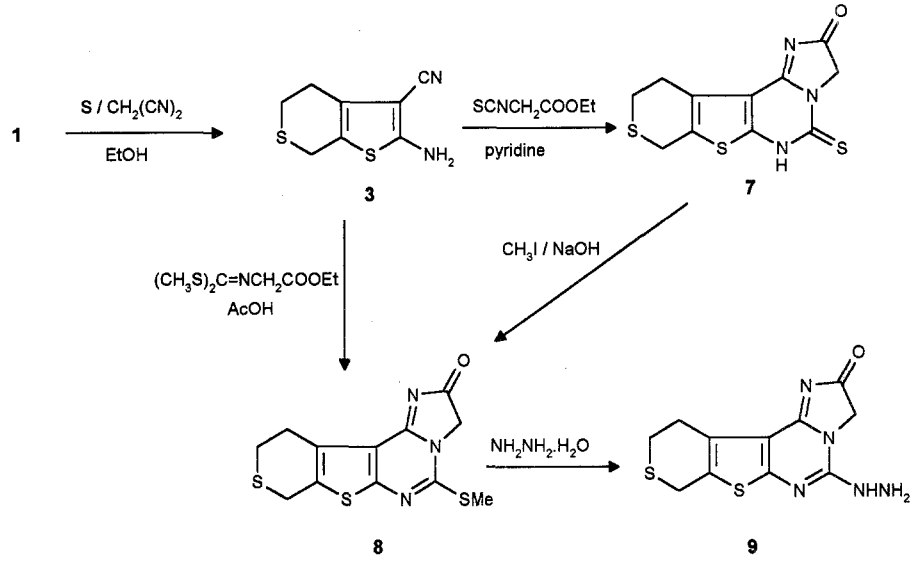
As illustrated in Scheme 3, the desired fusion can be achieved either by reacting **3** with isothiocyanatoacetate to yield **7**, an ensuing methylation of which leads to **8**, or by reacting **3** with the *BMMA* reagent $\mathbf{R}_1$ to yield **8** directly. In any case, the methylthio-group present in **8** can be replaced by reactive nucleophiles as illustrated with the synthesis of **9**.



5	n
a	1
b	2

6	n
a	1
b	2
c	3

Scheme 2



Scheme 3

Experimental

The melting points given were determined on a Kofler melting point apparatus and are uncorrected. Elementary analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. *J. Theiner*). ^{13}C and ^{1}H NMR spectra: Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz), 5 mm dual $^{1}H/^{13}C$-VT probe at 300 K; solvent: *DMSO*-d_6 and $CDCl_3$, respectively; δ values are given in ppm, internal standard *TMS* ($\delta = 0$ ppm). In some cases, due to low solubility no ^{13}C NMR spectra could be acquired on our spectrometer. IR-spectra were recorded on a Shimadzu 470 Spectrophotometer (KBr pellets).

5,8-Dihydro-2-(methylthio)-4-oxo-4H-thiopyrano[4',3':4,5]thieno[2,3-d]pyrimidin-3(6H)acetic acid ethyl ester (**4**)

A mixture of **2** (0.6 g, 2.4 mmol), N-(*bis*-(methylthio)-methylene)-glycine ethyl ester (0.51 g, 2.4 mmol) in dry AcOH (5 ml) was heated at 60–70 °C for 4 h under nitrogen. On cooling, the separated solid product was filtered, washed with ethanol, dried, and recrystallized from ethanol to yield 0.6 g (68% yield) of **4** as white crystals. M.p.: 233 °C; $C_{14}H_{16}N_2O_3S_3$ (356.47); calc.: C: 47.16, H: 4.52, N: 7.86; found: C: 46.91, H: 4.31, N: 7.68; IR (KBr): 1490, 1510, 1680, 1720, 2990, 3000 cm^{-1}; ^1H NMR ($CDCl_3$): 1.20 (t, 3 H, $-COOCH_2CH_3$), 2.60 (s, 3 H, SCH_3), 2.90 (t, 2 H, H-5), 3.30 (t, 2 H, H-6), 3.80 (s, 2 H, H-8), 4.20 (q, 2 H, $-COOCH_2CH_3$), 4.90 (s, 2 H, NCH_2COOEt); ^{13}C NMR (*DMSO*-d_6): 13.99 (q, SCH_3), 14.85 (q, $-COOCH_2CH_3$), 24.14 (t, C-4), 25.32 (t, C-5), 27.59 (t, C-7), 60.43 (t, NCH_2), 61.52 (t, $COOCH_2CH_3$), 111.46 (s, C-4a), 122.51 (s, C-4b), 129.91 (s, C-8a), 145.54 (s, C-9a), 164.64 (s, C-2), 167.39 (s, C-4), 187.73 (s, CO ester).

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

A mixture of **2** (0.48 g, 1.9 mmol) and 2-methylthio-2-thiazoline (0.28 g, 2.0 mmol) in dry AcOH (3 ml) was heated at 80 °C for 4 h. After cooling, the separated solid product was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol to give 1.5 g (68% yield) of **5a** as white crystals. M.p.: 199–201 °C; $C_{11}H_{10}N_2OS_3$ (282.39); calc.: C: 46.78, H: 3.56, N: 9.92; found: C: 46.72, H: 3.38, N: 9.92; IR (KBr): 1460, 1540, 1670, 2900, 3000 cm^{-1}; ^1H NMR (*DMSO*-d_6): 2.80 (t, 2 H, H-6), 3.10 (t, 2 H, H-7), 3.60 (t, 2 H, H-3), 3.80 (s, 2 H, H-9), 4.40 (t, 2 H, H-2); ^{13}C NMR (*DMSO*-d_6): 24.44 (t, C-6), 24.61 (t, C-7), 26.73 (s, C-9), 27.13 (t, C-2), 48.20 (t, C-3), 118.16 (s, C-5a), 126.86 (s, C-5b), 129.95 (s, C-9a), 156.24 (s, C-10a), 160.64 (s, C-12), 161.94 (s, C-5).

3,4,7,10-Tetrahydro-2H, 6H, 8H-thiopyrano[4'',3'':4',5']thieno[2',3':4,5]pyrimido[2,1-b][1,3]thiazin-6-one (**5b**)

A mixture of **2** (0.48 g, 2.0 mmol) and 2-methylthio-dihydro-1,3-thiazine (0.29 g, 2.0 mmol) in dry AcOH (4 ml) was heated at 80 °C for 3 h. After cooling, the separated solid product was collected, washed with ethanol, and recrystallized from ethanol to give 0.35 g (60% yield) of **5b** as yellow crystals. M.p.: 155–157 °C; $C_{12}H_{12}N_2OS_3$ (296.42); calc; C: 48.61, H: 4.08, N: 9.45; found: C: 48.42, H: 3.80, N: 9.22; ^1H NMR (*DMSO*-d_6): 2.20 (t, 2 H, H-3), 2.90 (t, 2 H, H-7), 3.20 (t, 2 H, H-8), 3.30 (t, 2 H, H-4), 3.80 (s, 2 H, H-10), 4.10 (t, 2 H, H-2).

1,3,4,7,8,9-Hexahydro-5H-pyrrolo[1,2-a]thiopyrano[4',3':4,5]thieno[2,3-d]pyrimidin-5-one (**6a**)

To 0.48 g (2.0 mmol) **2** and 0.19 g (2.2 mmol) pyrrolidone in 1,2-dichloroethane (5 ml), 5 drops of $POCl_3$ were added and the mixture was refluxed for 2 h. After evaporation of the solvent under reduced pressure, the residue was treated with ethanol, the solid product was collected by filtration, and recrystallized from ethanol to give 0.3 g (57% yield) of **6a** as white crystals. M.p.: 195–197 °C; $C_{12}H_{12}N_2OS_2$ (264.36); calc.: C: 54.51, H: 4.57, N: 10.59; found: C: 54.42, H: 4.41, N: 10.42; ^1H NMR ($CDCl_3$): 2.20–2.40 (m, 2 H, H-8), 2.90 (t, 2 H, H-4), 3.20 (t, 2 H, H-3), 3.40 (t, 2 H, H-9), 3.80 (s, 2 H, H-1), 4.20 (t, 2 H, H-7).

3,4,7,8,9,10-Hexahydro-1H, 5H-pyrido[1,2-a]thiopyrano[4',3':4,5]thieno[2,3-d]pyrimidin-5-one (**6b**)

Molar portions of amino ester **2** and valerolactam were treated as described for the preparation of **6a**. The yield of the crystallized compound was 67%. M.p.: 228–230 °C; $C_{13}H_{14}N_2OS_2$ (278.39); calc.: C: 56.08, H: 5.07, N: 10.06; found: C: 55.79, H: 4.87, N: 9.89; ^1H NMR ($CDCl_3$): 1.90–2.10 (m, 2 H, H-8), 2.90–3.10 (m, 4 H, H-4, H-3), 3.30 (t, 2 H, H-9), 3.90 (s, 2 H, H-1), 4.10 (t, 2 H, H-6); ^{13}C NMR

($CDCl_3$): 18.43 (t, C-9); 21.32 (t, C-8); 24.53 (t, C-4); 24.68 (t, C-3); 27.31 (s, C-1); 31.00 (t, C-10); 41.40 (t, C-7); 119.42 (s, C-4b); 127.05 (s, C-4a); 130.13 (s, C-12a); 156.03 (s, C-11a); 157.66 (s, C-10a); 160.65 (s, C-5).

1,3,4,7,8,9,10,11-Octahydro-5H-azepino[1,2-a]thiopyrano[4',3':4,5]thieno[2,3-d]pyrimidin-5-one (**6c**)

Upon treatment of amino ester **2** with caprolactam as described for the preparation of **6a**, 60% yield of recrystallized **6c** was obtained. M.p.: 171–173 °C; $C_{14}H_{16}N_2OS_2$ (292.41); calc.: C: 57.50, H: 5.51, N: 9.58; found: C: 57.72, H: 5.68, N: 9.78; ^{1}H NMR ($CDCl_3$): 1.70–1.90 (m, 6 H, H-7, H-8, H-9), 2.90 (t, 2 H, H-4), 3.00 (t, 2 H, H-3), 3.40 (t, 2 H, H-10), 3.80 (s, 2 H, H-1), 4.30 (t, 2 H, H-6).

6,8,10,11-Tetrahydro-5-thioxo-5H-imidazo[1,2-c]thiopyrano[4',3':4,5]thieno[3,2-e]pyrimidin-2(3H)-one (**7**)

A mixture of **3** (0.98 g, 5.0 mmol) and ethoxycarbonylmethyl isothiocyanate (0.73 g, 5.0 mmol) in dry pyridine (2 ml) was reflexed for 2 h under nitrogen. The solvent was removed under reduced pressure and the residue was treated with ethanol. The solid product was collected by filtration and recrystallized from ethanol to give 1.2 g (82% yield) of **7** as violet crystals. M.p.: 215 °C (dec.); $C_{11}H_9N_3OS_3$ (295.39); calc.: C: 44.72, H: 3.07, N: 14.22; found: C: 44.50, H: 3.13, N: 13.94; ^{1}H NMR (*DMSO*-d_6): 2.99 (t, 2 H, H-11), 3.10 (t, 2 H, H-10), 3.90 (s, 2 H, H-8), 4.40 (s, 2 H, H-3). 13.20 (bs, 1 H, NH).

10,11-Dihydro-5-(methylthio)-8H-imidazo[1,2-c]thiopyrano[4',3':4,5]thieno[3,2-e]pyrimidin-2(3H)-one (**8**)

Method A: A mixture of **3** (0.98 g, 5.0 mmol) and N-(*bis*-(methylthio)-methylene)-glycine ethyl ester (1.1 g, 5.2 mmol) in dry AcOH (3 ml) was heated at 70–75 °C for 6 h under nitrogen. After cooling, the solid product was collected by filtration, washed with ethanol, and recrystallized from ethanol to give 1 g (65% yield) of **8** as colorless crystals. M.p.: 278–280 °C (dec.); $C_{12}H_{11}N_3OS_3$ (309.42); calc.: C: 46.57, H: 3.58, N: 13.58; found: C: 46.65, H: 3.36, N: 13.32; IR (KBr): 1480, 1580, 1720, 2990 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): 2.65 (s, 3 H, SCH_3), 3.00 (t, 2 H, H-11), 3.20 (t, 2 H, H-10), 3.90 (s, 2 H, H-8), 4.30 (s, 2 H, H-3); ^{13}C NMR (*DMSO*-d_6): 13.69 (q, SCH_3), 24.50 (t, C-11), 24.60 (t, C-10), 27.11 (s, C-8), 49.74 (t, C-3), 114.24 (s, C-11b), 129.15 (s, C-11a), 129.38 (s, C-7a), 154.62 (s, C-6a), 162.41 (s, C-5), 164.90 (s, C-12), 183.66 (s, CO).

Method B: A solution of **7** (0.3 g, 1.0 mmol) in 1 *N* aqueous sodium hydroxide (10 ml) was treated with methyl iodide (0.3 g, 2.0 mmol) and the mixture was stirred at room temperature for 2 h. The solid product was collected by filtration, washed with water, dried, and recrystallized from ethanol to give 0.23 g (74% yield) of **8** as colorless crystals, m.p.: 278–280 °C (dec.). The compound is identical with the compound obtained above.

10,11-Dihydro-5-hydrazino-8H-imidazo[1,2-c]thiopyrano[4',3':4,5]thieno[3,2-e]pyrimidin-2(3H)-one (**9**)

A mixture of **8** (0.45 g, 1.0 mmol) and hydrazine hydrate (3 ml) in ethanol (10 ml) was refluxed for 50 minutes. After cooling, the solid product was collected by filtration, dried, and recrystallized from ethanol to give 0.39 g (93% yield) of **9** as colorless crystals. M.p.: 305 °C (dec.); $C_{11}H_{11}N_5OS_2$ (293.36); calc.: C: 45.03, H: 3.78, N: 23.87; found: C: 45.25, H: 3.68, N: 23.69; ^{1}H NMR (*DMSO*-d_6): 2.90 (t, 2 H, H-11), 3.20 (t, 2 H, H-10), 3.90 (s, 2 H, H-8), 4.30 (s, 2 H, H-3), 4.70 (bs, 2 H, NH_2), 8.90 (bs, 1 H, NH).

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