N-[BIS(METHYLTHIO)METHYLENE]AMINO ESTERS (BMMA): NOVEL REAGENTS FOR ANNELATION OF PYRIMIDINE MOIETIES[1]

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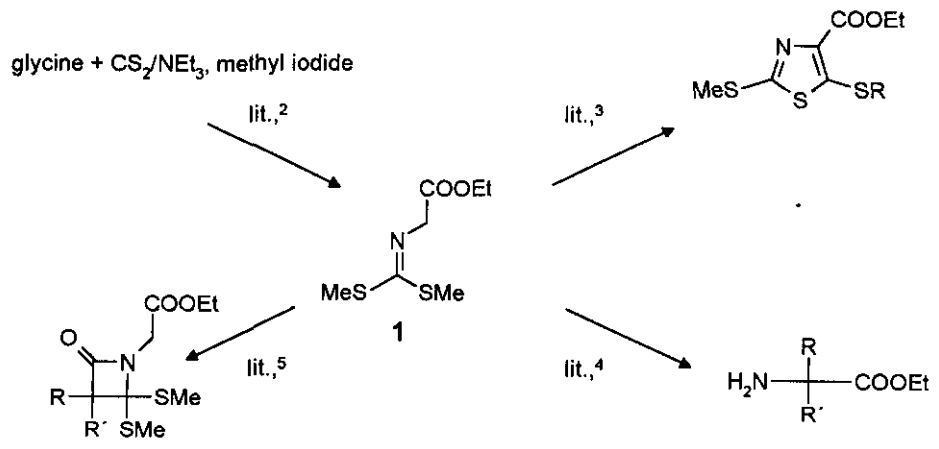
Abstract - New reagents for heterocyclic annelations containing a *N*-[**bis**(**me**thylthio)**me**thylene]**a**mino moiety (=BMMA) were developed and studied regarding their scope and limitations: one-pot reaction with (hetero)aromatic ortho-aminocarbonyl-type *model compounds* ("carbonyl" = COOEt, COMe and CN) to a series of new benzo- or thieno-condensed pyrimidines, pyrrolo[1,2-*c*]pyrimidines, *imidazo*[1,2-*c*]*pyrimidines* and 1,2,4-triazolo[1,5-c]pyrimidines, depending on the reagent used [$(MeS)_2C$=N-R with R = CH_2-*COOEt*, CH_2CH_2*COOEt*, NH-COOEt].

Dedicated to Prof. Huisgen with our very best wishes

INTRODUCTION

N-[Bis(methylthio)methylene]aminoacetic acid ethyl ester (**1**) has been synthesized by Hoppe[2] and was mainly employed in the literature for access to 1,3-thiazoles[3] or α-branched α-amino acids,[4]

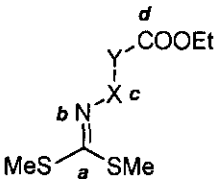
taking advantage of its various electrophilic and nucleophilic reaction sites and to lactam derivatives[5] *via* [2+2] cycloaddition strategies (*Scheme 1*):



Scheme 1

Our intention was to apply BMMA-esters to annelation reactions and to develop novel reagents derived from **1** in order to make new structural variations of the target compounds accessible. Whereas in published work cited above the main emphasis was concentrated on reactions at centres ***a*** and ***c***, our research was focused on annelation reactions to be carried out at positions ***a***,***b*** and ***d*** (*Figure 1*). Additionally, for generalized applicability new structurally modified reagents (**2**) and (**3**) were developed.

BMMA-Reagents:



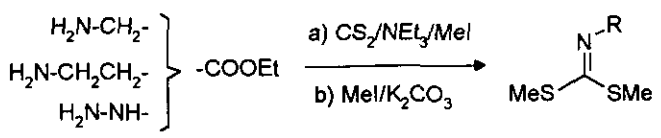
1 X, Y = CH_2
2 X = CH_2, Y = CH_2
3 X, Y = NH

Figure 1

SYNTHESES OF BMMA-REAGENTS (1 - 3)

N-[Bis(methylthio)methylene]glycine ethyl ester (**1**, "C_1-reagent"), 3-amino-*N*-[bis(methylthio)-methylene]propionic acid ethyl ester (**2**, "C_2-reagent") and *N*-[bis(methylthio)methylene]hydrazine-carboxylic acid ethyl ester (**3**, "N_1-reagent) were prepared in analogy to Hoppe[2] by reacting adequate

amino educts with $CS_2/NEt_3/MeI$ and subsequently accomplishing the alkylation of the intermediates thus obtained with MeI/K_2CO_3 (*Scheme 2*).



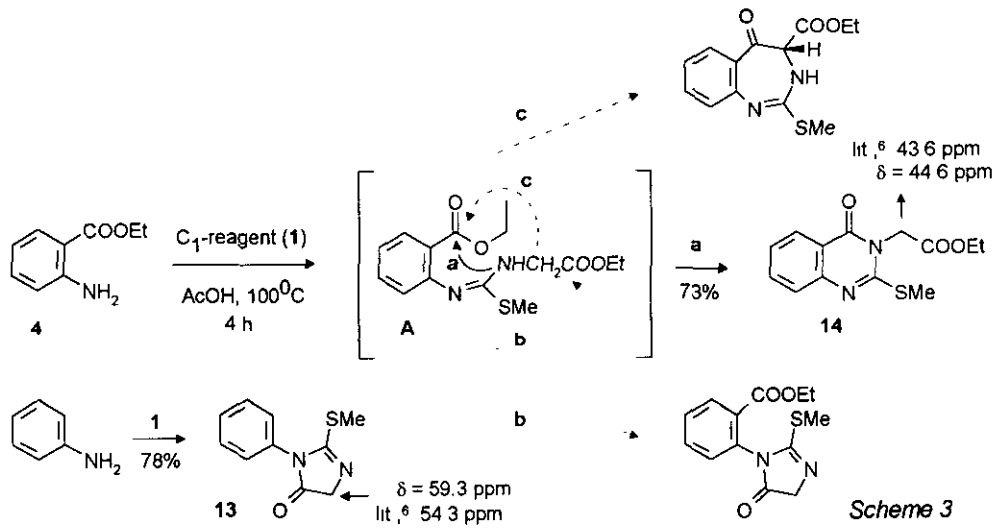
	R	yield (%)
1	CH_2COOEt	87
2	CH_2CH_2COOEt	73
3	NHCOOEt	82

Scheme 2

RESULTS AND DISCUSSION

Reactions of 1- 3 with Aromatic *ortho*-Amino Esters

2-Aminobenzoic acid ethyl ester (**4**) was reacted with **1** at 100 °C in AcOH as a solvent (*Scheme 3*).



Scheme 3

For intermediate **A** (obtained by an addition-elimination) there are 3 principal possibilities for an ensuing cyclization: pathway **c** - *via* an ester-condensation reaction - would have led to a 7-membered system, which could be clearly excluded due to lack of the indicated C-H in proton-nmr-spectra. Moreover, even under basic reaction conditions (EtOH/NaOEt, $N(Et)_3$) no benzodiazepine was formed. Products from pathways **a** and **b** containing the same structural elements are making a differentiation at first glance not so easy, but possibility **b** could be ruled out by several items of

evidence: comparison of ^{13}C-shifts of **14** with nmr data of 3,4-dihydro-2-methyl-4-oxoquinazoline-3-acetic acid (retrieved from a ^{13}C-data bank[6]) and of phenylimidazole (**13**), prepared from aniline and C_1-reagent (**1**), gave an unequivocal indication for pathway **a** (selected carbon shifts see: *Scheme 3*).

Via this method a series of heterocyclic compounds (**14** - **19**) were accessible from various (hetero)arylamines (*Table 1*), no cyclizations were observed starting from non-aromatic open-chain enaminoesters as $H_2N\text{-}C(R^1)\text{=}CH\text{-}COOEt$ (R^1 = Me, COOEt).

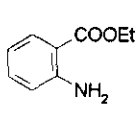
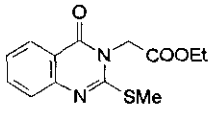
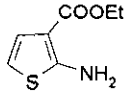
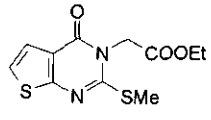
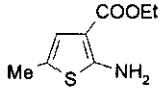
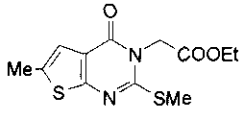
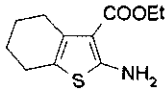
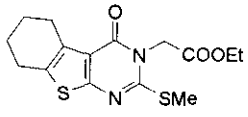
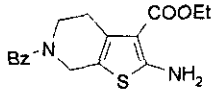
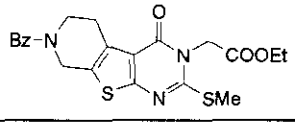
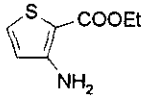
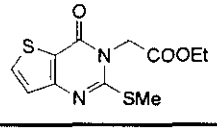
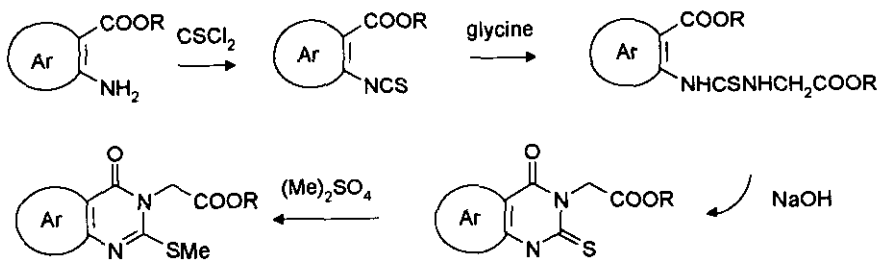
Starting Compound	*Conditions*	*Product*	*Yield*
4 	4 h, reflux temperature	**14** 	73%
5 	2 h, reflux temperature	**15** 	62%
6 	3 h, reflux temperature	**16** 	79%
7 	3 h, reflux temperature	**17** 	73%
8 	4 h, reflux temperature	**18** 	40%
9 	4 h, reflux temperature	**19** 	71%

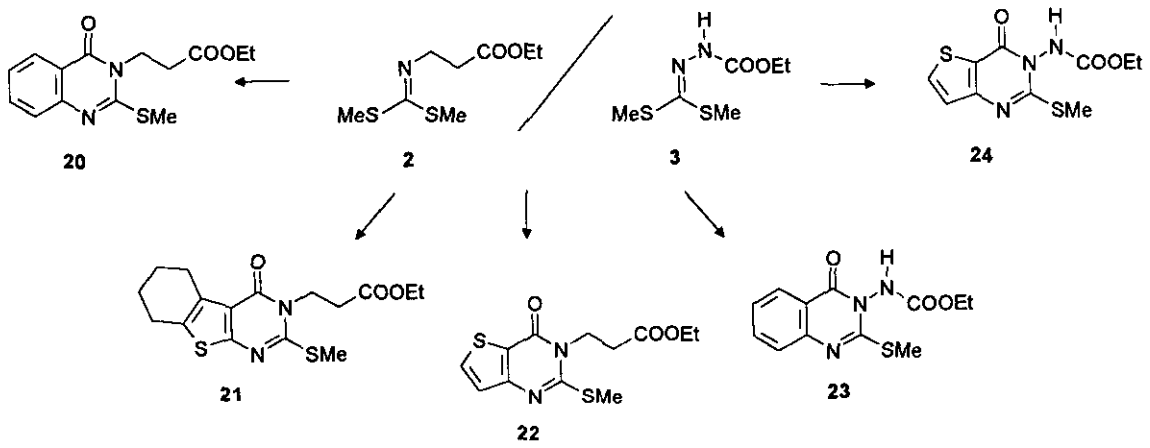
Table 1

Utilization of the C_1-reagent allows one-pot annelation of a pyrimidine moiety with a complex and useful substitution pattern, thus being advantageous over a multi-step pathway to analogous compounds published in literature[7] (*Scheme 4.*)



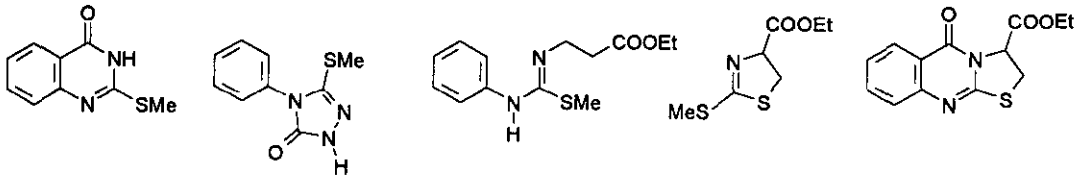
Scheme 4

The new reagents (**2**) and (**3**) also proved to be useful when reacted with enamino ester-type educts: cyclizations led to compounds (**20** - **24**) with *different* substituents at position 3 (yields: 62-75%; *Scheme 5*).



Scheme 5

Alkaline work-up as applied to reactions with C_1- and N_1-reagents (**1**) and (**3**) had to be avoided in the case of the C_2-reagent due to product decomposition to **25**, caused by retro-Michael type elimination of acrylic ester. Reaction with aniline (under equal conditions as reported for the C_1-reagent) to obtain products for comparison of nmr-data led to aza-analogous compounds (**26**) when utilizing the N_1-reagent (**3**), but stopped at an open chain intermediate (**27**) when subjected to the C_2-reagent:

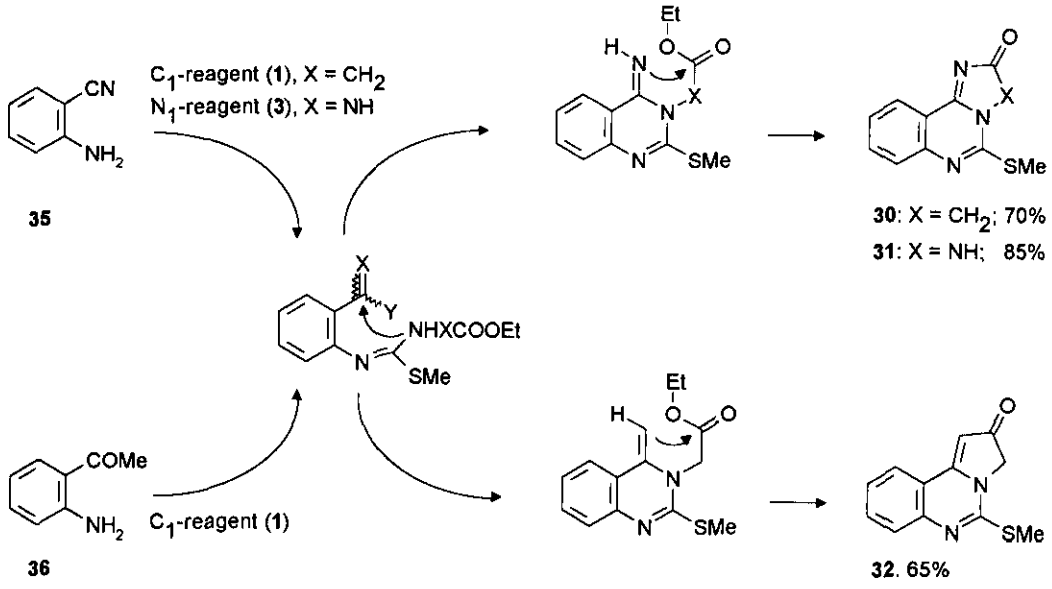


25 **26** **27** **28** **29**

To extend the scope of the BMMA-reagents the reactive sites were also incorporated into a cyclic system as depicted by compound (**28**):[8] indeed, starting from anthranilic ester (**4**) the thiazolo-fused target compound (**29**) was obtained in one pot reaction (yield: 57%).

Reactions of 1- 3 with Aromatic *ortho*-Aminonitriles and -ketones

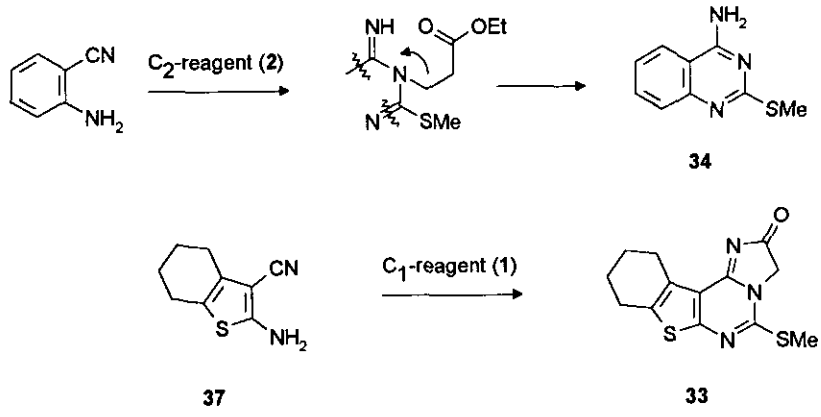
A new and smooth access to novel tricyclic hetero-compounds was made possible *via* one-pot tandem-annelation of pyrrolo[1,2-*c*]pyrimidine, imidazo[1,2-*c*]pyrimidine and 1,2,4-triazolo[1,5-*c*]pyrimidine moieties to (hetero)aromatic *ortho*-aminocarbonyl or *ortho*-aminonitrile systems as starting material: (*Scheme 6*): reaction of 2-aminobenzonitrile (**35**) and 2-aminoacetophenone (**36**) with the C_1- and N_1-reagents (**1**, **3**) in AcOH led to target compounds (**30** - **32**).



Scheme 6

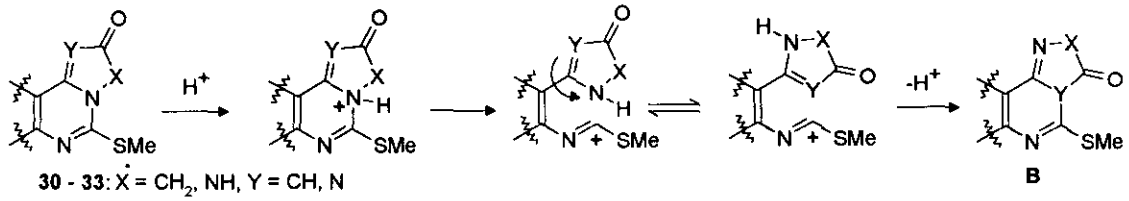
When starting from 2-amino-4,5,6,7-tetrahydro-2-benzo[*b*]thiophenecarbonitrile (**37**), *compound* **33** was obtained (yield: 59%).

While treatment of 2-amino-acetophenon with C_2- or N_1-reagents (**1**, **3**) resulted in decomposition, 2-aminobenzonitrile and C_2-reagent (**2**) yielded the quinazoline (**34**), obviously due to retro-Michael elimination of acrylic ester prior to a consecutive annelation reaction in analogy to findings cited above (*Scheme 7*).



Scheme 7

The correctness of the constitutions given for compounds (**30** - **33**) was critically checked mainly by nmr spectroscopic methods. The reason for being very cautious is that under the reaction conditions applied (i.e. AcOH) the principal possibility of a *Dimroth*-type rearrangement[9] has to be considered In such as case products of type **B** as depicted in *Scheme 8* would be formed.



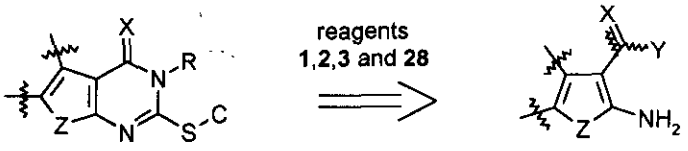
Scheme 8

For products (**32**) (X = CH_2, Y = CH) the constitution was unambiguously proved from ^{1}H-nmr spectra: the proton at the pyrrole moiety appeared as a singlet and not as a triplet as to be

postulated for type **B**. Structures (**30**) and (**33**) (X = CH_2, Y = N) were proved by NOE between the CH_2 of the imidazole-moiety and the SMe-substituent. Additional strong support comes from the significant low ^{13}C-shift of the pyrazolone-carbonyl group at 183.9 ppm: on the one hand, estimation from increments[10] results in 190 ppm, whereas a C=O-group of type **B** would demand for ca. 170 ppm, and on the other hand ^{13}C-data bank[6] retrieval led to hits with R'(RNH)C=N-$COCH_3$-moieties (being sub-structures of **30** and **33**) exhibiting C=O shifts ranging from 185.1 - 187.5 ppm. The constitution given for the triazolo derivative (**31**) (X = NH, Y = N) is additionally confirmed by mechanistic arguments: similar fused compounds have been reported to be the thermodynamically most stable products.[11]

CONCLUSION

By reacting (hetero)aromatic *ortho*-aminocarbonyl educts with the BMMA-reagents (**1**, **2**, **3** and **28**) a series of new annelated heterocyclic compounds are obtained smoothly and in good yields in one-pot reactions, as depicted in a generalized form in *Scheme 9*.



Z = CH=CH, S; X = C, O, N; Y = O;

Scheme 9

Investigations to extend the applicability of these reagents to various other heteroaromatic starting materials are currently in progress.[12]

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). Tlc: Tlc-layers with SiO_2 60 F_{254}, Merck Art.-Nr.

5554; eluents: petroleum ether (PE); ethyl acetate (EA); triethylamine (TEA); benzene (Bz); ether (Et_2O). "Flash"-chromatography: SiO_2 60 F_{254}, Merck Art.-Nr. 9385, particle size: 0.040-0.063 mm, pressure. 1 bar; 50 g SiO_2 in 450 x 25 mm glass columns. ^{13}C- and ^1H-nmr spectra: Bruker AC 200 (^1H: 200.13 MHz, ^{13}C: 50 47 MHz), 5 mm dual $^1H/^{13}C$-VT-probe head at 300 K; solvent. DMSO-d_6 and $CDCl_3$, respectively; δ values are given ppm, internal standard TMS (δ = 0 ppm); 2-aminobenzoic acid ethyl ester, 2-aminobenzonitrile and 2-aminoacteophenone were purchased from Aldrich; all thiophene-derived enaminoesters and nitriles were prepared according to general Gewald-procedures.[13]

General Procedure for the Syntheses of BMMA-reagents (1 - 3): The starting amino ester (500 mmol; for synthesis of **1** : glycine ethyl ester hydrochloride; for synthesis of **2** : β-alanine ethyl ester hydrochloride; for synthesis of **3** : hydrazine carboxylic acid ethyl ester), CS_2 (40.0 g, 500 mmol) and triethyl amine (106.0 g, 1050 mmol) were reacted at 40 °C in chloroform (500 ml) for 1 h. After addition of MeI (177.2 g, 1250 mmol) the mixture was heated at reflux temperature for 1 h. For work-up the solution was cooled and extracted with ether. After washing with water (100 ml) the organic layer was dried (Na_2SO_4) and evaporated. Subsequently the crude oil was dissolved in acetone (300 ml), K_2CO_3 (100 g, 724 mmol) and MeI (85.2 g, 600 mmol) were added and the mixture was heated for 3 h at reflux temperature, followed by stirring at room temperature over night For work-up the precipitated salts were filtered off, most of the acetone was removed in vacuo, water was added and the product was extratced with ether. After drying (Na_2SO_4), evaporation and destillation products (**1** - **3**) were obtained as colorless oils. The yields are given in *Scheme* 2, the physical properties are listed below.

***N-[Bis(methylthio)methylene]glycine Ethyl Ester* (1):** bp 96-98 °C (0.08 mm Hg); Rf = 0.75 (Bz/Et_2O=5:1), ^1H-nmr ($CDCl_3$): δ 4.29 (q, J = 7 1 Hz, 2H), 4.24 (s, 2H), 2.56 (s, 3H), 2 45 (s, 3H), 1 28 (t, J = 7.1 Hz, 3H).

***3-Amino-N-[bis(methylthio)methylene]propanoic Acid Ethyl Ester* (2):** bp 104-106 °C (0.04 mm Hg); Rf = 0 65 (Bz/Et_2O=5:1); ^1H-nmr ($CDCl_3$): δ 4.14 (q, J = 7.1 Hz, 2H), 3 65 (t, J = 7.2 Hz,2H), 2.66 (t, J = 7.2 Hz,2H), 2.54 (s, 3H), 2.32 (s, 3H), 1 25 (t, J = 7 1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 172.0 (s),

158.42 (s), 60.0 (t), 48.38 (t), 35.76 (t), 14.4 (q), 14.25 (q), 14.09 (q); Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.41; H, 6.83; N, 6.33. Found: C, 43.22; H, 6.88; N, 6.15.

***N-[Bis(methylthio)methylene]hydrazine Carboxylic Acid Ethyl Ester* (3):** bp 113-115 ^{0}C (0.02 mm Hg); Rf = 0.55 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 8.2 (br s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.49 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 153.0 (s), 145.36 (s), 61.28 (t), 15.33 (q), 14.57 (q), 14.09 (q); Anal. Calcd for $C_6H_{12}N_2O_2S_2$: C, 34.60; H, 5.81; N, 13.45. Found: C, 34.66; H, 5.89; N, 13.51.

General Procedure for Cyclization and Annelation Reactions: Equimolar Amounts of BMMA-reagent (**1**, **2**, **3** or **28**) and appropriate starting compound (see *Table 2*) were heated in AcOH (1 ml per 1 mmol educt) at reflux temperature (different reaction temperatures and times. see *Table 2*). After cooling the reaction mixture was worked up according to following methods: ***A*** - after dilution with water (10 fold) the precipitate was filtered with suction and triturated with or recrystallized from the solvent given in; ***B*** - evaporation of AcOH followed by Kugelrohr distillation and / or recrystallition; ***C*** - dilution with water (10 fold) and extraction with methylene chloride (M), ether (E) or ethyl acetate (EA), *products (**13**, **27**): pH=8 (NaOH) during work-up. Reaction details are given in *Table* 2, the physical properties of the target compounds are listed below.

***2-(Methylthio)-3-phenylimidazol-4(5H)-one* (13):** yellow crystals, mp 79 - 82 °C, Rf = 0.15 (Bz/Et_2O=4:1); ^{1}H-nmr ($CDCl_3$): δ 7.60 - 7.20 (m, 5H), 4.34 (s, 2H), 2 51 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 178.8 (s), 163.8 (s), 132.2 (s), 129.4 (d), 129.1 (d), 127.3 (d), 59.3 (t), 12.7 (q).

***3,4-Dihydro -2-(methylthio)-4-oxoquinazoline-3-acetic Acid Ethyl Ester* (14):** colorless crystals after trituration with n-hexane, mp 107 - 109 °C (EtOH); Rf = 0.5 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 8.25-8.13 (m, 1H), 7.75-7.29 (m, 3H), 4.90 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 166.6 (s), 161.0 (s), 156.15 (s), 147.2 (s), 134.15 (d), 126.78 (d), 125.97 (d), 125.43 (d), 118.7 (s), 61.55 (t), 44.6 (t), 14.74 (q), 13.8 (q).

***3,4-Dihydro-2-methylthio-4-oxothieno[2,3-d]pyrimidine-3-acetic Acid Ethyl Ester* (15):** beige crystals after trituration with 2-butanone, mp 91 - 95 °C; Rf = 0.8 (PE/EA=3:2); ^{1}H-nmr ($CDCl_3$): δ 7.39 (d, J = 6Hz, 1H), 7.09 (d, J = 6Hz, 1H), 4.91 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 2.65 (s, 3H), 1.37

(t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 166.6 (s), 163.63 (s), 157.66 (s), 122.12 (d), 121.2 (d), 119.9 (s), 61 77 (t), 44.54 (t), 15.11 (q), 13.92 (q).

Educt	*BMMA*	*Conditions*	*Work-up*	*Product*	*Yield*
aniline	**1**	4 h	***A, C*** (E)*	**13**	78%
4	**1**	4 h	***A***	**14**	73%
5	**1**	2 h	***C*** (M)	**15**	62%
6	**1**	3 h	***A***	**16**	79%
7	**1**	3 h	***A***	**17**	73%
8	**1**	4 h	***B***	**18**	40%
9	**1**	4 h	***A***	**19**	71%
4	**2**	4 h, 70 °C	***C*** (E)	**20**	74%
7	**2**	6 h	***A***	**21**	73%
9	**2**	6 h, 60 °C	***A***	**22**	75%
4	**3**	4 h, 70 °C	***B***	**23**	70%
9	**3**	10 h	***A***	**24**	62%
aniline	**3**	2 h, 50 °C	***C*** (M)	**26**	79%
aniline	**2**	2 h, room temperature	***C*** (M)*	**27**	84%
4	**28**	5 h, 50 °C	***C*** (EA)	**29**	57%
35	**1**	2 h	***A***	**30**	70%
35	**3**	36 h, 80 °C	***B***	**31**	85%
36	**1**	2 h	***A***	**32**	65%
37	**1**	3 h	***A***	**33**	59%
35	**2**	12 h, 80 °C	***C*** (E)	**34**	89%

Table 2

***3,4-Dihydro-6-methyl-2-methylthio-4-oxothieno[2,3-d]pyrimidine-3-acetic Acid Ethyl Ester* (16):** orange crystal from isopropanole, mp 130 - 131 °C (i-PrOH); Rf = 0.6 (Bz/Et_2O=5:1); ^{1}H-nmr (DMSO-d_6): δ 7.10 (q, J = 1.1 Hz, 1H), 4.84 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 2.54 (d, J = 1.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C-nmr (DMSO-d_6): δ 166.7 (s), 161.83 (s), 157.45 (s), 156.2 (s), 136.1 (s), 119.57 (s), 118.92 (d), 61.44 (t), 44.6 (t), 15.28 (q), 14.79 (q), 13.87 (q).

***3,4,5,6,7,8-Hexahydro-2-methylthio-4-oxo-[1]benzthieno[2,3-d]pyrimidine-3-acetic Acid Ethyl Ester* (17):** beige crystals after trituration with diisopropyether, mp 149-150 °C; Rf = 0.75 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 4.86 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.00-2.70 (m, 4H), 2.61 (s, 3H), 1.45-1.30 (m, 4H), 1.29 (t, J = 7.1 Hz,3H) ^{13}C-nmr ($CDCl_3$): δ 166.88 (s), 162.21 (s), 157 83 (s), 156.26 (s), 131.55 (s), 131.33 (s), 118.27 (s), 61 77 (t), 44.32 (t), 25.36 (t), 25.0 (t), 22.92 (t), 22.21 (t), 15.12 (q), 14.03 (q).

***3,4,5,6,7,8-Hexahydro-2-methylthio-4-oxo-7-phenylmethylpyrido[4',3':4,5]thieno[2,3-d]pyrimidine-3(4H)-acetic Acid Ethyl Ester* (18):** yellowish crystals from ethanol, mp 151-152 °C (EtOH); Rf = 0.25 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 7.40-7 25 (m, 5H), 4.86 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.73 (s, 2H), 3.63 (s, 2H), 3.20-3.10 (m, 2H), 2.95-2.85 (m, 2H), 2.61 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 166.82 (s), 162.7(s), 157.83 (s), 156.8 (s), 137 9 (s), 129.76 (s), 129.0 (d), 128.3 (d), 127.22 (d), 117.9 (s), 61.82 (t), 51.42 (t), 49.74 (t), 44.32 (t), 25 2 (t), 15.17 (q), 14.03 (q); Anal. Calcd for $C_{21}H_{23}N_3O_3S_2$: C, 58.72; H, 5.40; N, 9.78. Found: C, 58.64, H, 5.33; N, 9.81

***3,4-Dihydro-2-methylthio-4-oxothieno[3,2-d]pyrimidine-3-acetic Acid Ethyl Ester* (19):** yellowish crystals after trituration with diisopropyether, mp 136-138 °C .(i-PrOH); Rf = 0.6 (PE/EA=2:1); ^{1}H-nmr ($CDCl_3$): δ 7.39 (d, J = 6Hz, 1H), 7.10 (d, J = 6Hz, 1H), 4.91 (s, 2H), 4 27 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.33 (q, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 166.6 (s), 158.58 (s), 157.49 (s), 156.14 (s), 134.3 (d), 124.34 (d), 118.82 (s), 61.77 (t), 44.43 (t), 15.17 (q), 13.92 (q).

***3,4-Dihydro-2-methylthio-4-oxoquinazoline-3-propanoic Acid Ethyl Ester* (20):** colorless, crystallizing oil after Kugelrohr distillation, bp (Kugelrohr) 140-145 °C (0.03 mm Hg); mp 63-65 °C; Rf = 0.5 (PE/EA=6:1); ^{1}H-nmr ($CDCl_3$): δ 8 25-8.10 (m, 1H), 7.75-7.27 (m, 3H), 4.55-4.29 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.9-2 68 (m, 2H), 2.66 (s, 3H), 1.25 (t, J = 7 1 Hz, 3H), ^{13}C-nmr ($CDCl_3$/DMSO-d_6): δ 169.15 (s), 160.35 (s), 155.28 (s), 146.1 (s), 134 15 (d), 125.37 (d), 124.88 (d),

124.4 (d), 117.8 (d), 59.49 (t), 38.9 (t), 31.21 (t), 13.7 (q), 12.95 (q); Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.31; H, 5.63; N, 9.32.

***3,4,5,6,7,8-Hexahydro-2-methylthio-4-oxo-[1]benzothieno[2,3-d]pyrimidine-3-propanoic Acid Ethyl Ester* (21):** cololess crystals after trituration with diisopropylether, mp 121-124 °C; Rf = 0.8 (PE/EA=3:1); ^{1}H-nmr ($CDCl_3$): δ 4.47-4.29 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.15-2.67 (m, 6H), 2.60 (s, 3H), 1.90-1.75 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 170 34 (s), 161.9 (s), 157.78 (s), 156.0 (s), 131.22 (s), 131.0 (s), 118.27 (s), 60.57 (t), 39 61 (t), 32.13 (t), 25.25 (t), 24.87 (t), 22.81 (t), 14.84 (q), 13.92 (q); Anal. Calcd for $C_{16}H_{20}N_2O_3S_2$: C, 54.52; H, 5.72; N, 7.82. Found: C, 54.69; H, 5.76; N, 7.97.

***3,4-Dihydro-2-methylthio-4-oxothieno[3,2-d]pyrimidine-3-propanoic Acid Ethyl Ester* (22):** colorless crystals after trituration with diisopropylether, mp 115 °C (EtOH); Rf = 0 5 (Bz/EtOH=9:1); ^{1}H-nmr ($CDCl_3$): δ 7.72 (d, J = 5Hz, 1H), 7.19 (d, J = 5Hz, 1H), 4.55-4.35 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.94-2.71 (m, 2H), 2.63 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 170.23 (s), 158.48 (s), 157.61 (s), 155.93 (s), 149.59 (d), 134.0 (d), 124.23 (s), 60.68 (t), 40.0 (t), 32.24 (t), 15.0 (q), 14.0 (q); Anal. Calcd for $C_{16}H_{20}N_2O_3S_2$: C, 48.30; H, 4.73; N, 9.39. Found: C, 48.51; H, 4.85; N, 9.22.

***N-[3,4-Dihydro-2-methylthio-4-oxoquinazoline-3-yl]carbaminic Acid Ethyl Ester* (23):** colorless oil after Kugelrohr distillation, bp (Kugelrohr) 170-180 °C (0.03 mm Hg); Rf = 0.3 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 8.20-8.10 (m, 1H), 7.90-7.60 (m, 2H), 7.50-7.25 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 2.55 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$): δ 160.1 (s), 159.3 (s), 155.06 (s), 147.31 (s), 134.69 (d), 127.0 (d), 126.35 (d), 125.48 (d), 119.25 (s), 63.0 (t), 14.19 (q), 14.09 (q); Anal. Calcd for $C_{12}H_{13}N_3O_3S$ x 0.25 H_2O· C, 50.80; H, 4.79; N, 14.81. Found: C, 50.79; H, 4.74; N, 14.80.

***N-[3,4-Dihydro-2-methylthio-4-oxothieno[3,2-d]pyrimidine-3-yl]carbaminic Acid Ethyl Ester* (24):** beige crystals after recrystallization from ethyl acetate; mp 80-83 °C (EA); Rf = 0.5 (PE/EA=4:1); ^{1}H-nmr ($CDCl_3$/DMSO-d_6): δ 7.57 (d, J = 5Hz, 1H), 7.00 (d, J = 5Hz, 1H), 3.95 (q, J = 7 1 Hz, 2H), 2.3 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$/DMSO-d_6): δ 162.33 (s), 155.82 (s), 155.71 (s), 155.06 (s), 134.8 (d), 124.45 (d), 118.38 (s), 62.0 (t), 14.1 (q); Anal. Calcd for $C_{16}H_{20}N_2O_3S_2$: C, 42.09; H, 3.89; N, 14.73. Found: C, 42.38; H, 4.00; N, 14.51.

***5-Methylthio-4-phenyl-1H[1,2,4]triazole-3(4H)-one* (26):** colorless crystals after trituration with diisopropyl ether; mp 205-206 °C; Rf = 0.2 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$/DMSO-d_6): δ 12.50 (br s,

1H), 7.50-7.30 (m, 5H), 2.64 (s, 3H); ^{13}C-nmr ($CDCl_3$/DMSO-d_6): δ 154.1 (s), 143.4 (s), 132.1 (s), 128.7 (d), 128.1 (d), 126.1 (d), 12.7 (q); Anal. Calcd for $C_9H_9N_3OS$ x 0.23 H_2O: C, 51.14; H, 4.51; N, 19.68. Found: C, 51.32; H, 4.34; N, 19.36.

***3-Amino-N-[(N'-phenylamino)methylthiomethylen]propanoic Acid Ethyl Ester* (27):** yellowish oil; Rf = 0.45 (Bz/Et_2O=5:1); ^{1}H-nmr ($CDCl_3$): δ 7.36-7.10 (m, 2H), 7.06-6.76 (m, 3H), 4.7 (br s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.76-3.5 (m, 2H), 2.74-2.54 (m, 2H), 2.27 (s, 3H), 1,27 (t, J = 7.1 Hz, 2H); ^{13}C-nmr ($CDCl_3$): δ 172.45 (s), 152.8 (s), 149.43 (s), 128.73 (d), 122.5 (d), 122.0 (d), 60.57 (t), 38.52 (t), 33.86 (t), 14.09 (q), 13.82 (q).

***2,3-Dihydro-5-oxo-5H-thiazolo[2,3-b]quinazoline-3-carboxylic Acid Ethyl Ester* (29):** colorless crystals after flash chromatography (1g crude product/20 g SiO_2; eluent· PE/EA=2:1); mp 76-78 °C; DC: Rf = 0.3 (PE/EA=2:1); ^{1}H-nmr ($CDCl_3$): δ 8.28-8.13 (m, 1H), 7.83-7.31 (m, 3H), 5.56 (dd, J_{XA} = 3 Hz, J_{XB} = 8.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.83 (dd, J_{BX} = 8.8 Hz, J_{AB} = 12Hz, 1H), 3.53 (dd, J_{AX} = 3 Hz, J_{AB} = 12Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C-nmr ($CDCl_3$/DMSO-d_6): δ 167.25 (s), 159.13 (s), 158.75 (s), 148.29 (s), 134.26 (d), 125.81 (d), 125.43 (d), 118.33 (s), 61.71 (t), 60.09 (d), 28.88 (t), 13.49 (q); Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10 14. Found: C, 56.63; H, 4.35; N, 9.96.

***5-Methylthioimidazo[1,2-c]quinazoline-2(3H)-one* (30):** slightly pink crystals from isopropanol, mp 238-240 °C (n-PrOH); Rf = 0.1 (Bz/Et_2O=5.1); ^{1}H-nmr (DMSO-d_6). δ 7.85-7.80 (m, 1H), 7.57-7.10 (m, 3H), 4.26 (s, 2H), 2.65 (s, 3H); ^{13}C-nmr ($CDCl_3$/DMSO-d_6)· δ 183.87 (s), 169 85 (s), 152.27 (s), 146.9 (s), 135.5 (d), 131.6 (d), 126.35 (d), 126 0 (d), 113.6 (s), 50.38 (t), 13.11 (q); Anal. Calcd for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18 17. Found: C, 57 04; H, 4.02; N, 17.99.

***4-Methylthio[1,2,4]triazolo[1,5-c]quinazoline-2(3H)-one* (31):** yellowish crystals after trituration with Et_2O/i-PrOH; mp 240 °C (decomp); ^{1}H-nmr (DMSO-d_6): δ 8.32-8.13 (m, 1H), 7.95-7.38 (m, 3H), 3.30 (br s, 1H), 2 70 (s, 3H); ^{13}C-nmr (DMSO-d_6): δ 168.37 (s), 149.16 (s), 148.7 (s), 142.9 (s), 132.2 (d), 127.05 (d), 123.2 (d), 114.26 (s), 12.89 (q); Anal. Calcd for $C_{10}H_8N_4OS$ x 0.25 H_2O: C, 50.75; H, 3.62; N, 23.60. Found: C, 50.88; H, 3.45; N, 23.34.

***2-Methylthiopyrrolo[1,2-c]quinazoline-5(4H)-one* (32):** beige crystals after trituration with diisopropyl ether; mp 107 - 109 °C; Rf = 0.2 (PE/EA=2:3); ^{1}H-nmr ($CDCl_3$): δ 7.70-7.20 (m, 4H), 5.73 (s, 1H), 4.16 (s, 2H), 2.68 (s, 3H); ^{13}C-nmr ($CDCl_3$): δ 192.50 (s), 165.52 (s), 153.38 (s), 144.61 (s),

134.04 (d), 126.46 (d), 125.81 (d), 125.64 (d), 115 57 (s), 94.11 (d), 54.78 (t), 13.27 (q); Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.46; H, 4.24; N, 11.96.

***5-Methylthio-8,9,10,11-tetrahydro[1]benzthieno[3,2-d]imidazo[1,2-c]pyrimidine-2(3H)-one* (33):** colorless crystals after trituration with ethanol; mp 170 °C (DMF) (decomp.); ^{1}H-nmr (DMSO-d_6): δ 4.33 (s, 2H), 2.85-2.70 (m, 4H), 2.67 (s, 3H), 1.95-1.80 (m, 4H); ^{13}C-nmr ($CDCl_3$): δ 169.31 (s), 162.21 (s), 60.14 (t) 53.75 (t), 14.36 (q), 14.0 (q), 13.72 (q); Anal. Calcd for $C_{13}H_{13}N_3OS_2$: C, 53.59; H, 4.50; N, 14.42. Found: C, 53.52; H, 4 35; N, 14.57.

***4-Amino-2-methylthioquinazoline* (34):** beige crystals after trituration with isopropanol; mp 230-233 °C; ^{1}H-nmr ($CDCl_3$): δ 8.17-8.00 (m, 1H), 7.78-7.16 (m, 3H), 2.52 (s, 3H); ^{13}C-nmr (DMSO-d_6): δ 167.0 (s), 160.9 (s), 150.0 (s), 132.9 (d), 125.9 (d), 123.9 (d), 123.64 (d), 112.64 (s), 13.11 (q), Anal. Calcd for $C_9H_9N_3S$. C, 56 52; H, 4.74; N, 21.97. Found: C, 56.60; H, 4.80; N, 21.79.

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REFERENCES

1. Part of this work has been presented at the 3rd Blue Danube Symposium On Heterocyclic Chemistry, Sopron, Hungary, 1993.
2. D. Hoppe and L. Beckmann, Liebigs Ann Chem., **1979**, 2066.
3. C. Alvarez-Ibarra, E. Davila, A. Mateo, P. Ortiz, and M. L. Quiroga, Tetrahedron Lett., **1987**, 6667.
4. D. Hoppe, Angew. Chemie, *1975*, **87**, *450*.
5. D. F. Sullivan, D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, J. Org. Chem., 1976, **41**, 1112
6. H. Kalchhauser and W. Robien, J. Chem. Inform. Comput. Sci., 1985, **25**, 103.
7. F. Kienzle, A. Kaiser, and E. Minder, Helv. Chim. Acta, 1983, **66**, 148.

8. Y. Nagao, T. Kumagai, S. Takao, T. Abe, M. Ochiai, T. Taga, Y. Inoue, and E. Fujita, J. Org. Chem., 1986, **51**, 4739.

9. M. Künstlinger and E. Breitmaier, Synthesis, 1983, **14**, 44; C. J. Shishoo, M B. Devani, G. V. Ullas, S. Anathan, and V. S. Bhadti, J. Heterocycl. Chem., 1981, **18**, 43; C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Anathan, and V. S. Bhadti, J. Heterocycl. Chem., 1987, **24**, 1125.

10. C-13 Module for ChemWindow for Windows 3.1x, Release 3.0, SoftShell International, 1600 Ute Avenue, Grand Junction, CO 81501-4614, 1994.

11. H. Breuer, Tetrahedron Lett., **1976**, 1935.

12. Synthesis of Some Novel Tetracyclic Systems by Annelation of An Imidazo Moiety, F. Sauter, J. Fröhlich, and A. Z. M. S. Chowdhury, Poster presented at 4th Blue Danube Symposium On Heterocyclic Chemistry, 22nd - 25th June 1994, St. Pölten, Austria.

13. K. Gewald, E. Schinke, and H. Bottcher, Chem. Ber., 1966, **99**, 94.

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