Methanetricarboxylates as Key Reagents for the Simple Preparation of Heteroarylcarboxamides with Potential Biological Activity. Part 2 [1]. Reaction of Methanetricarboxylates with 2-Aminopyridine, 2-Aminopyrimidine, 2-Aminothiazole and 2-Aminobenzothiazole

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Dedicated to Professor Henk C. van der Plas on the occasion of his 70th birthday

The reaction of methanetricarboxylates **1a,b** with 2-aminopyridine, 2-aminopyrimidine, 2-aminothiazole as well as 2-aminobenzothiazole yields corresponding heteroarylcarboxylic acid esters **2a,b, 5, 8, 11a,b**. These heterocyclic esters were used as a starting material by the reaction with primary amines to obtaining a number of heteroarylcarboxylic amides **4a-j, 6, 10a,b, 13a-g** bearing various substituents on the carboxamide group.

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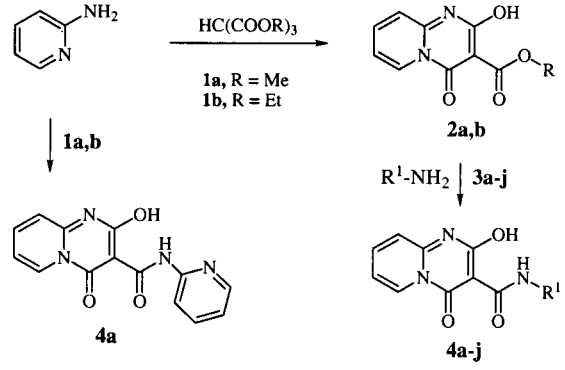
"Cyclic tricarbonylmethane derivatives" play an important role in agricultural chemistry, whether they are carbocyclic or heterocyclic, oximated or not [1-4]. We have recently shown that the reaction of methanetricarboxylates with substituted cyclic anilines (such as indolenine and 1,2,3,4-tetrahydroquinoline) leads to heterocyclic carboxylic acid esters and amides with a cyclic tricarbonyl methane moiety [1]. It is known that this type of compounds, especially the amides, show very potent antiinflammatory [5], high antimicrobial and fungicidal [6], anticoagulant [7], or herbicidal [8] activitiy. Our long lasting interest [9] in the synthesis of potential anti-inflammatory and herbicidal heterocycles has prompted us to study the reaction of aromatic 2-amino-*N*-heterocycles, such as 2-aminopyridine, 2-aminopyrimidine, 2-aminothiazole and

Scheme 1



R[1] Key see Table 1

Table 1

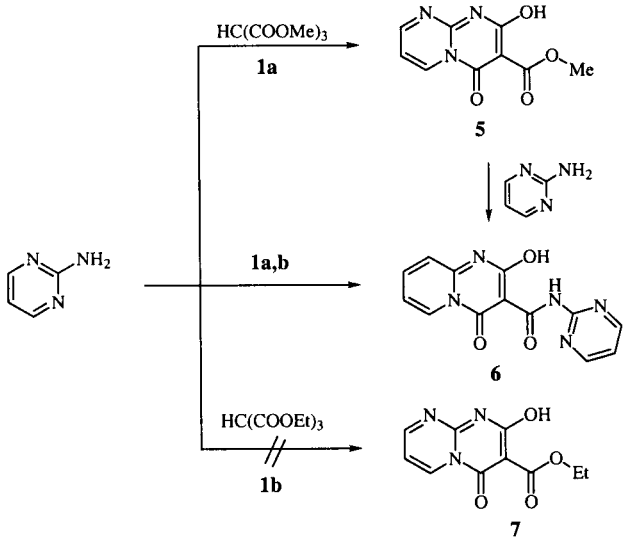
Experimental, Physical and Analytical Data of Compounds **4**

No.	R[1]	Reaction Time, Method A (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis Calcd./Found C	H	N
4a	2-Pyridyl	8	43	250 (dimethylformamide)	$C_{14}H_{10}N_4O_3$	59.57 59.68	3.57 3.70	19.85 19.75
4b	Ph	10	59	226 (dimethylformamide)	$C_{15}H_{11}N_3O_3$	64.05 64.37	3.94 4.01	14.94 15.25
4c	4-Me-Ph	12	68	262 (dimethylformamide)	$C_{16}H_{13}N_3O_3$	65.08 64.89	4.44 4.20	14.23 14.76
4d	3-MeO-Ph	20	56	265 (dimethylformamide)	$C_{16}H_{13}N_3O_4$	61.73 61.47	4.21 4.06	13.50 13.34
4e	4-Cl-Ph	24	76	288 (dimethylformamide)	$C_{15}H_{10}ClN_3O_3$	57.07 56.89	3.19 3.25	13.31 13.59
4f	2,6-Di-Me-Ph	30	72	317 (dimethylformamide)	$C_{17}H_{15}N_3O_3$	66.01 66.13	4.89 4.95	13.58 13.80
4g	2,6-Di-MeO-Ph	30	49	188 (dimethylformamide)	$C_{17}H_{15}N_3O_5$	59.82 60.05	4.43 4.33	12.31 12.49
4h	2,6-Di-Cl-Ph	36	50	256 (dimethylformamide)	$C_{15}H_9Cl_2N_3O_3$	51.45 51.59	2.59 2.53	12.00 12.01
4i	2-Pyrimidyl	2	80	262 (dimethylformamide)	$C_{13}H_9N_5O_3$	55.13 55.36	3.20 3.25	24.73 24.64
4j	2-Benzothiazolyl	12	75	318 (dimethylformamide)	$C_{16}H_{10}N_4O_3S$	56.80 56.43	2.98 2.81	16.56 15.98

2-aminobenzothiazole, with methanetricaboxylates **1a,b**, and to prepare the corresponding amides.

The reaction of equimolar amounts of methanetricarboxylic acid esters **1a,b** and 2-aminopyridine does not yield the esters **2a** and **2b** but rather the amide **4a**. The yield can be of course improved if a small excess of aminopyridine is used. This is in accordance with our previous results [1]. The esters **2a,b** can only be obtained if at least a twofold excess of methanetricarboxylates **1a,b** [10] is employed. Refluxing bromobenzene has been used as the solvent for this reaction. Once at hand, esters **1a,b** could be successfully condensed with a number of aromatic and heteroaromatic amines to afford the 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides **4a-j**. Again bromobenzene was used as solvent, and the reaction times are given in Table 1.

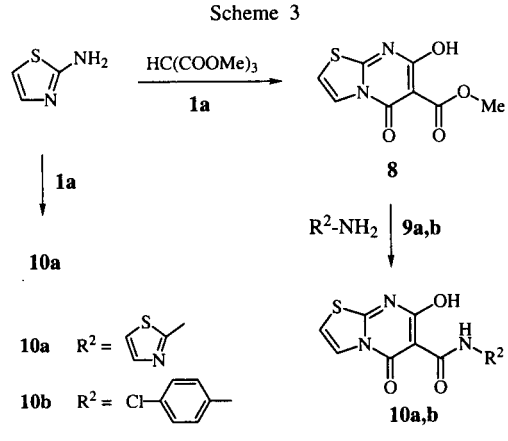
Scheme 2



In a similar manner 2-aminopyrimidine has been allowed to react with **1** to afford the ester **5** and the amide **6**. However, the bicyclic heterocyclic ester **7** could not be obtained starting with **1b** (Scheme 2).

The fused ester **8** has been obtained from 2-amino-1,3-thiazole (**9a**) with an excess of methyl methanetricarboxylate **1a**. Again, equimolar amounts of the reactants led to **10a**, and amide **10b** was obtained from the reaction of **1a** with 4-chloroaniline (**9b**) in refluxing bromobenzene (Scheme 3).

Scheme 3



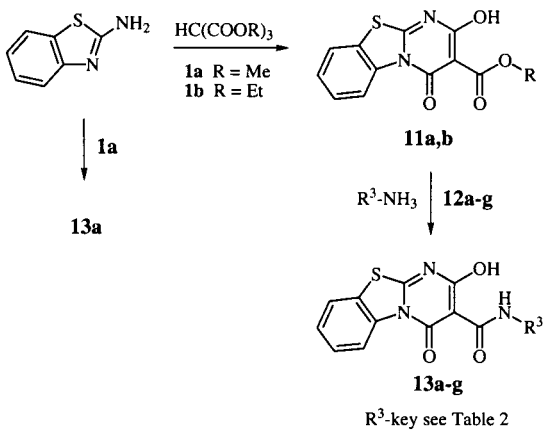
The reaction of 2-aminobenzothiazole with excess of **1a,b** afforded the stable heteroarylcarboxylic esters **11a** and **11b** in yields of 52% and of 55%, respectively. Their condensation with some aliphatic, aromatic and heteroaromatic amines produced the carboxamides **13a-g** (Scheme 4). Again, compound **13a** was also prepared by the direct condensation of 2-aminobenzthiazole with **11a** and **11b**. For reaction conditions, yields, physical and analytical data see Table 2.

Table 2

Experimental, Physical and Analytical Data of Compounds **13**

No.	R^1	Reaction Time, Method A (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis Calcd./Found C	H	N
13a	2-Benzothiazolyl	14	52	340 (dimethylformamide)	$C_{18}H_{10}N_4O_3S_2$	54.81 54.78	2.56 2.30	14.21 14.01
13b	*tert*-Butyl	10	67	270 (hexane)	$C_{15}H_{15}N_3O_3S$	56.77 56.80	4.76 4.65	13.24 13.21
13c	4-Me-Ph	24	71	236 (dimethylformamide)	$C_{18}H_{13}N_3O_3S$	61.53 61.35	3.73 3.65	11.96 11.76
13d	4-Cl-Ph	28	71	258 (dimethylformamide)	$C_{17}H_{10}ClN_3O_3S$	54.92 54.66	2.71 2.66	11.30 11.18
13e	3-CF_3-Ph	30	75	204 (dimethylformamide)	$C_{18}H_{10}F_3N_3O_3S$	53.34 53.33	2.49 2.48	10.37 10.43
13f	2-Pyridyl	10	73	301 (dimethylformamide)	$C_{16}H_{10}N_4O_3S$	56.80 56.60	2.98 2.95	16.56 16.48
13g	2-Thiazolyl	10	59	276 (dimethylformamide)	$C_{14}H_8N_4O_3S$	53.84 53.60	2.58 2.58	17.94 17.65

Scheme 4



EXPERIMENTAL

Melting points were obtained on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. The ir spectra were recorded on a Perkin-Elmer Model 298 infrared spectrophotometer in potassium bromide pellets. The nmr spectra were measured on a Varian Gemini 200 and a Bruker AM 360 spectrometer with tetramethylsilane as internal standard. The solvent for nmr was hexadeuteriodimethyl sulfoxide unless otherwise stated. Microanalyses were performed on a Carlo Erba 1106 Elemental analyzer. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Preparation of ethyl and methyl methanetricarboxylates **1a,b** were performed according to the literature [10].

General Procedure for the Preparation of Esters **2a,b**, **5**, **8**, **11a,b**.

Esters **1a** or **1b** (10 mmoles) and the appropriate amine (2-aminopyridine, 2-aminopyrimidine, 2-aminothiazole or 2-aminobenzothiazole), 5 mmoles, in bromobenzene (50 ml) were heated under reflux for the time given. The solvent was evaporated under reduced pressure. Products **2a,b**, **5**, **8**, and **11a,b** were crystallized from the appropriate solvents.

Methyl 2-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2a**).

The reaction time was 6 hours, yield 51%, mp 246° (1-propanol); ir: ν 3050 (OH), 1700, 1650 (C=O, C=C) cm^{-1}; ^1H nmr: δ 3.70 (s, 3H, OCH_3), 7.50, 8.25 (m, 3H, aromatic), 9.0 (dd, 1H, J = 7 and 2 Hz).

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.23; H, 3.61; N, 12.89.

Ethyl 2-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2b**).

The reaction time 6 was hours, yield 68%, mp 210° (1-propanol); ir: ν 3050 (OH), 1700, 1650 (C=O, C=C) cm^{-1}; ^1H nmr: δ 1.25 (t, 3H, J = 7 Hz, CH_3), 4.25 (q, 2H, J = 7 Hz, CH_2), 7.40, 8.25 (m, 3H, aromatic), 9.0 (dd, 1H, J = 7 and 2 Hz).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.52; H, 4.25; N, 11.80.

Methyl 2-Hydroxy-4-oxo-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (**5**).

The reaction time was 10 hours, yield 62%, mp 224° (dimethyl sulfoxide); ir: ν 3000 (OH), 1720, 1700 (C=O, C=C) cm^{-1}; ^1H nmr: δ 3.70 (s, 3H, CH_3), 7.6, 9.10 (m, 2H, aromatic), 9.35 (dd, 1H, J = 7 and 2 Hz).

Anal. Calcd. for $C_9H_7N_3O_4$: C, 48.88; H, 3.19; N, 19.00. Found: C, 48.97; H, 3.42; N,18.99.

Methyl 7-Hydroxy-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**8**).

The reaction time was 7 hours, yield 61%, mp 189° (1-propanol); ir: ν 3200, 3180 (OH), 1725, 1640 (C=O, C=C) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.10 (s, 3H, OCH_3), 7.1 (d, 1H, J = 4Hz, =CH), 8.1 (d, 1H, J = 4Hz, =CH), 13.9 (s, 1H, OH).

Anal. Calcd. for $C_8H_6N_2O_4S$: C, 42.48; H, 2.67; N, 12.38. Found: C, 42.20; H, 2.58; N, 12.57.

Methyl 2-Hydroxy-4-oxo-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (**11a**).

The reaction time was 5 hours, yield 52%, mp 210° (1-propanol); ^1H nmr: δ 4.10 (s, 3H, OCH_3), 7.5 (m, 3H, aromatic), 9.10 (m, 1H, aromatic), 13.95 (s, 1H, OH).

Anal. Calcd. for $C_{12}H_8N_2O_4S$: C, 52.17; H, 2.92; N, 10.14. Found: C, 51.91; H, 2.83; N, 9.96.

Ethyl 2-Hydroxy-4-oxo-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (**11b**).

The reaction time was 5 hours, yield 55%, mp 200° (1-propanol); ^1H nmr: δ 1.50 (t, 3H, J = 7 Hz, CH_3), 4.60 (q, 2H, J = 7 Hz, CH_2), 7.5 (m, 3H, aromatic), 9.10 (dd, 1H, J = 7 and 2 Hz) 14.1 (s, 1H, OH).

Anal. Calcd. for $C_{13}H_{10}N_2O_4S$: C, 53.79; H, 3.47; N, 9.65. Found: C, 53.74; H, 3.45; N, 9.60.

General Procedure for the Preparation of Amides **4a-j**, **6**, **10a,b**, **13a-g**.

Method A.

The esters **2a,b**, **5**, **8**, or **11a,b** (5 mmoles) and amines **3a-j**, **9a,b**, **12a-g** or 2-aminopyrimidine (7 mmoles) were heated in bromobenzene (35 ml) under reflux. The solvent was evaporated under reduced pressure. The amides **4a-j**, **6**, **10a,b**, **13a-g** were crystallized. See Tables 1 and 2.

Method B.

The esters **1a** or **1b** (5 mmoles) and the appropriate amines (2-aminopyridine, 2-aminopyrimidine, 2-aminothiazole or 2-aminobenzothiazole) (10 mmoles) were heated at 200° for 20 minutes without solvent. The amides **4a**, **6**, **10a** and **13a** were crystallized. See Tables 1 and 2. The yield of amides **4a**, **6**, **10a** and **13a** were 92, 89, 98 and 96%, respectively.

*N*3-(Pyrimidin-2-yl)-2-hydroxy-4-oxopyrimido[1,2-*a*]pyrimidinecarboxamide (**6**).

The reaction time was 10 hours (method A) and 0.3 hour (method B), yield 48% (method A), 89% (method B), mp dec >360° (dimethyl sulfoxide); ir: ν 3000 (OH, NH), 1740, 1700, 1620 (C=O, C=C) cm^{-1}; ^1H nmr: δ 7.25, 7.70 (m, 3H, aromatic), 8.0 (m, 1H, aromatic), 8.70 (m, 2H, aromatic).

Anal. Calcd. for $C_{12}H_8N_6O_3$: C, 50.7; H, 2.84; N, 29.57. Found: C, 51.05; H, 2.70; N, 29.20.

*N*6-(1,3-Thiazol-2-yl)-7-hydroxy-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidinecarboxamide (**10a**).

The reaction time was 8 hours (method A) and 0.3 hour (method B), yield 63 (method A), 98% (method B), mp 269° (dimethylformamide); ir: ν 3050 (OH, NH), 1680, 1620, 1565 (C=O, C=C) cm^{-1}.

Anal. Calcd. for $C_{10}H_6N_4O_3S_2$: C, 40.81; H, 2.06; N, 19.04. Found: C, 40.60; H, 1.99; N, 19.01.

*N*6-(4-Chlorophenyl)-7-hydroxy-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidinecarboxamide (**10b**).

The reaction time was 12 hours (method A), yield 65%, mp 303° (dimethylformamide); ir: ν 3100 (OH, NH), 1680, 1630 (C=O, C=C) cm^{-1}.

Anal. Calcd. for $C_{13}H_8ClN_3O_3S$: C, 48.53; H, 2.51; N, 13.06. Found: C, 48.65; H, 2.58; N, 13.14.

*N*3-(Benzo[*d*][1,3]thiazolyl)-2-hydroxy-4-oxo-4*H*-benzo[4,5]-thiazolo[3,2-*a*]pyrimidinecarboxamide (**13a**).

For experimental, physical and analytical data see Table 2; ir: ν 3200, 2950 (OH, NH), 1670 (C=O, C=C) cm^{-1}.

Compound **13b** had ^1H nmr of δ 1.50 (s, 9H, CH_3), 7.60 (m, 1H, aromatic), 8.10 (m, 1H, aromatic), 8.90 (m, 1H, aromatic), 9.60 (m, 1H, aromatic).

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[9] See reference [1], footnotes [6-8].

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