Synthesis of Substituted [1]Benzothieno[2,3-*b*]pyrazines

Sergio Cannizzo, Francesco Guerrera* and Maria Angela Siracusa

Istituto di Chimica Farmaceutica e Tossicologica, Università di Catanie,
V.le Andrea Doria 6, 95125 Catania, Italy

Antonino Corsaro

Dipartimento di Scienze Chimiche, V.le Andrea Doria 6,
95125 Catania, Italy

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The synthesis of a series of novel 1-unsubstituted and 1-alkyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-*b*]-pyrazine-2,3-diones **4a-d** and their corresponding dialkylaminoalkylamino derivatives **6a-d** starting from 2-nitro-3-bromobenzo[*b*]thiophene is described. The title ring system has not been reported previously.

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Recently our researches have been devoted to the synthesis of condensed tricyclic systems of potential biological activity with a thiophene ring as a central nucleus [1-7]. After we have dealt with the construction at the C_2-C_3 bond of benzo[*b*]thiophene of five-membered rings containing nitrogen atoms such as imidazole [2,6,7] and triazole [6] ring, we turned our interest to benzothienopyrazine derivatives which appear to have received little attention. The only reports found concern the synthesis of [1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines [8,9] and dibenzo[*f*,*h*][1]benzothieno[2,3-*b*]quinoxalines [10]. The [1]benzothieno[2,3-*b*]pyrazine ring system has not been reported.

As the first derivatives we decided to prepare 1-unsubstituted and 1-alkyl-1,2,3,4-tetrahydro [1]benzothieno-[2,3-*b*]pyrazine-2,3-diones **4a-d** and the 3-dialkylaminoalkylamino[1]benzothieno[2,3-*b*]pyrazin-2(1*H*)-ones **6a-d** for a comparison of their pharmacological properties with those of already known analogues containing the pyrimidine [11-15] and the pyridazine nucleus [16-18].

The synthesis of diones **4a-d** was performed as shown in the Scheme starting from ethyl *N*-H and *N*-alkyl(2-nitrobenzo[*b*]thien-3-yl)oxalinates **2a-d**, which were easily obtained by the bromine replacement of 2-nitro-3-bromobenzo[*b*]thiophene with ammonia or the appropriate alkylamines in *N*,*N*-dimethylformamide at 80° followed by the treatment of the resulting 3-amino derivatives **1a-d** with ethyl oxalyl chloride in dioxane at room temperature. A reductive cyclization of compounds **2a-d** into the diones **4a-d** by using molecular hydrogen in the presence of palladium on charcoal in glacial acetic acid and also in *N*,*N*-dimethylformamide following Loev's conditions [19] to obtain the corresponding hydroxamic acids, were initially attempted, but surprisingly, in both cases mixtures of products were obtained and the separation was not tried because of the very poor yields of the desired compounds. Good yields (~80%) of diones **4a-d** were achieved by reduction of oxalinates **2a-d** with sodium dithionite, followed by exposure of the resulting amino derivatives **3a-d** to hydrochloric acid. On keeping at 50° the mixture resulting from the addition of an aqueous solution of sodium dithionite to a hydroalcoholic or water/dioxane

Scheme

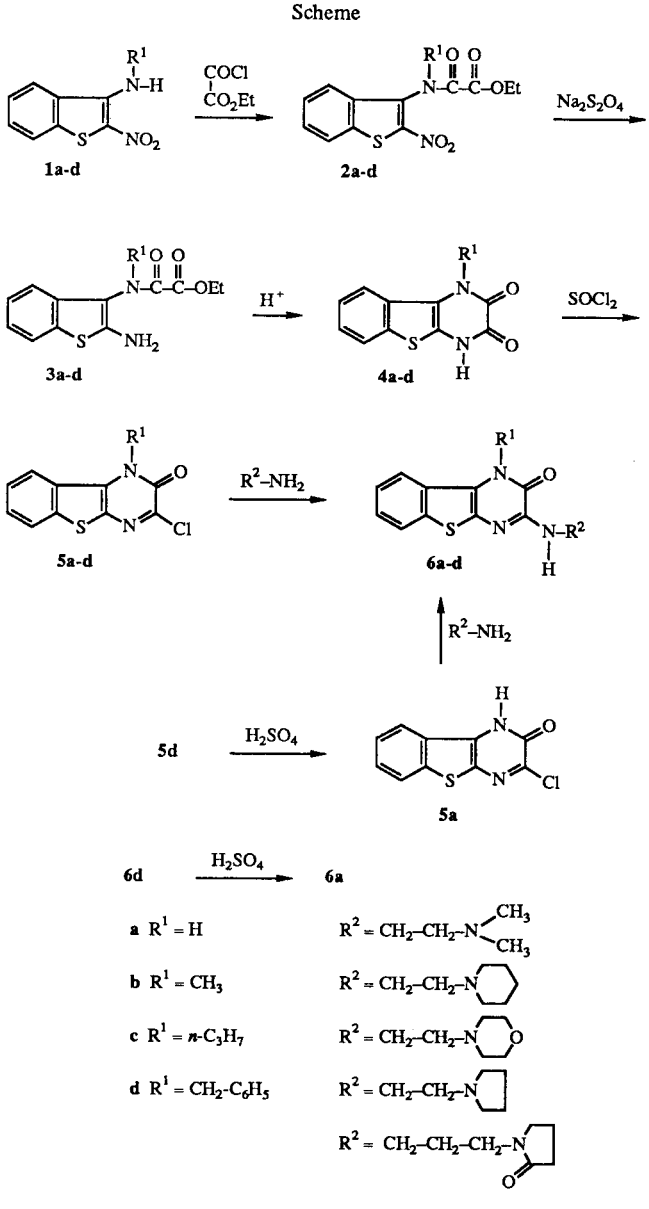
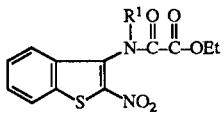


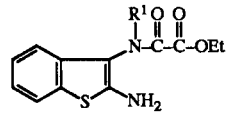
Table 1

Ethyl *N*H- and *N*-Alkyl-*N*-(2-nitrobenzo[b]-thien-3-yl)oxalinates **2a-d**



2a-d

Ethyl *N*H- and *N*-Alkyl-*N*-(2-aminotrobenzo[b]-thien-3-yl)oxalinates **3a-d**

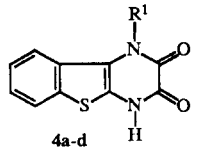


3a-d

Compound	R^1	Yield %	Mp °C (solvent)	IR (cm^{-1})	Molecular Formula	Microanalytical Data (%) (Calcd./Found) C	H	N
2a	H	80	180-182 (Acetone)	3360, 1740, 1540, 1370	$C_{12}H_{10}N_2O_5S$ (294.28)	48.97 48.95	3.42 3.37	9.51 9.40
2b	CH_3	82	134-136 (EtOH)	1750, 1710, 1540, 1340	$C_{13}H_{12}N_2O_5S$ (308.30)	50.64 50.51	3.92 3.90	9.08 9.10
2c	*n*-C_3H_7	87	82-84 (Cyclohexane)	1765, 1680, 1540, 1340	$C_{15}H_{16}N_2O_5S$ (336.36)	53.56 53.40	4.79 4.71	8.32 8.00
2d	$CH_2C_6H_5$	85	90-92 (Cyclohexane)	1760, 1680, 1540, 1340	$C_{19}H_{16}N_2O_5S$ (384.40)	59.36 59.20	4.19 4.10	7.28 7.02
3a	H	86	161-163 (Cyclohexane)	3420, 3360, 3320, 1760, 1685	$C_{12}H_{12}N_2O_3S$ (264.29)	54.53 54.40	4.57 4.47	10.59 10.35
3b	CH_3	88	145-147 (Cyclohexane)	3460, 3360, 3250, 1740, 1680	$C_{13}H_{14}N_2O_3S$ (278.32)	56.10 55.95	5.07 5.00	10.06 9.98
3c	*n*-C_3H_7	85	180-182 (Cyclohexane)	3460, 3360, 3240, 1760, 1650	$C_{15}H_{18}N_2O_3S$ (306.38)	58.80 58.72	5.92 5.94	9.14 9.12
3d	$CH_2C_6H_5$	90	132-134 (Cyclohexane)	3440, 3360, 3245, 1750, 1650	$C_{19}H_{18}N_2O_3S$ (354.42)	64.38 64.27	5.11 5.06	7.90 7.85

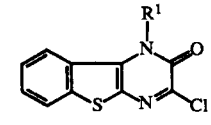
Table 2

1-Unsubstituted and 1-Alkyl 1,2,3,4-tetrahydro[1]benzo-thieno[2,3-*b*]pyrazine-2,3-diones **4a-d**



4a-d

1-Unsubstituted and 1-Alkyl -3-chloro[1]benzo-thieno[2,3-*b*]pyrazin-2(1*H*)-ones **5a-d**



5a-d

Compound	R^1	Yield %	Mp °C (solvent)	Molecular Formula	M^+ (%)	Microanalytical Data (%) (Calcd./Found) C	H	N
4a	H	75	>260	$C_{10}H_6N_2O_2S$ (218.20)	218 (85)	55.03 55.10	2.77 2.80	12.83 12.75
4b	CH_3	82	>260	$C_{11}H_8N_2O_2S$ (232.25)	232 (100)	56.88 56.50	3.47 3.30	12.06 12.00
4c	*n*-C_3H_7	75	>260	$C_{13}H_{12}N_2O_2S$ (260.31)	260 (90)	59.98 59.77	4.64 4.57	10.76 10.78
4d	$CH_2C_6H_5$	80	>260	$C_{17}H_{12}N_2O_2S$ (308.35)	308 (69)	66.21 66.01	3.92 3.85	9.08 9.00
5a	H	98	>260 (EtOH)	$C_{10}H_5N_2ClOS$ (236.67)	236 (100) 238 (82)	50.74 50.80	2.12 2.09	11.83 11.67
5b	CH_3	90	>260 (Toluene)	$C_{11}H_7N_2ClOS$ (250.70)	250 (70) 252 (80)	52.70 52.50	2.81 2.68	11.17 11.07
5c	*n*-C_3H_7	85	167-169 (EtOH)	$C_{13}H_{11}N_2ClOS$ (278.75)	278 (92) 280 (75)	56.01 55.90	3.97 3.94	10.04 9.90
5d	$CH_2C_6H_5$	87	204-206 (EtOH)	$C_{17}H_{11}N_2ClOS$ (326.80)	326 (80) 328 (65)	62.48 62.30	3.39 3.25	8.57 8.50

solution of nitrooxalinates **2a-d**, the corresponding amino derivatives **3a-d** were obtained in ~86% yields. These latter compounds readily cyclized to give diones **4a-d** by exposure to glacial acetic acid.

The isolation step of the amino derivatives **3a-d** was necessary to obtain pure diones because of the large amounts of sulfur which coprecipitates when the reduction mixtures are acidified and heated.

The preparation of dialkylaminoalkylamines **6a-d** required the conversion of diones **4a-d** into the corresponding chloro derivatives **5a-d** from which the first are smoothly obtained by nucleophilic substitution reactions of the halogen atom with the appropriate amine.

Thionyl chloride proved to be an efficient chlorinating agent for compounds **4b-d** and the chloro derivatives **5b-d** were isolated with good yields (~90%). Because of the improbability of performing a selective chlorination of the 3-carbon atom of the pyrazine nucleus in derivative **4a** with thionyl chloride treatment, the synthesis of 3-chloro-[1]benzothieno[2,3-*b*]pyrazin-2(1*H*)-one **5a** was achieved from the 1-benzyl-3-chloro[1]benzothieno[2,3-*b*]pyrazin-2(1*H*)-one **5d** following the known method based on the heterolysis reaction of the C-N bond which tertiary amides undergo upon exposure to concentrated sulfuric acid at room temperature [20]. The yield was of 98%.

Table 3

^{1}H NMR data of 1-Unsubstituted and 1-Alkyl-3-chloro[1]benzothieno[2,3-*b*]pyrazin-2(1H)ones **5a-d**

Compound	R^1	δ H6	δ H7,8	δ H9	δ Other protons
5a [a]	H	8.31	7.62, 7.56	8.09	NH, 13.82
5b	CH_3	8.31	7.56, 7.53	7.95	CH_3, 4.21
5c	*n*-C_3H_7	7.99	7.54, 7.52	7.87	CH_2, 4.59, 1.97; CH_3, 1.15
5d	$CH_2C_6H_5$	7.93	7.46, 7.20 [b]	7.83	CH_2, 5.89

[a] In dimethyl sulfoxide-d_6. [b] Multiplet integrating for 7H (benzothiophene H-7 and H-8, and phenyl-H).

The structures of all compounds synthesized were confirmed by mass spectra and analytical data (Tables 2, 4). The reduction of nitro derivatives **2a-d** was substantiated by the ir spectra (Table 1). The structures of chloro derivative **5a-d** were also confirmed by ^{1}H nmr spectroscopy (Table 3).

Furthermore the structure of the *N*-unsubstituted 3-chloro derivative **5a** was confirmed by its conversion into the corresponding amino derivative **6a** was identical with those obtained from the sulfuric acid induced debenzylation of compounds **6d**.

EXPERIMENTAL

All the melting points were taken on a Büchi 510 apparatus and are uncorrected. Elemental analysis were performed on a Carlo Erba elemental analyzer 1106, the ir spectra were obtained on a Perkin-Elmer spectrophotometer 281, using samples in potassium bromide disks. The ^{1}H nmr spectra were recorded on a Bruker AC 80 spectrometer operating at 80 MHz in deuteriochloroform solution unless otherwise stated, using TMS as the internal standard. Mass spectra were run on a Carlo Erba/Kratos MS 25RFA instrument at 70 eV ionization energy by a direct inlet system.

General Procedure for the Preparation of 2-Nitro-3-alkylbenzo[*b*]thiophenes **1a-d**.

A solution of 2-nitro-3-bromobenzo[*b*]thiophene [21] (10 mmoles) and an excess (40 mmoles) of the appropriate alkylamine in *N*,*N*-dimethylformamide (50 ml) was kept at 60° until all the starting benzothiophene was consumed (approximatively 15 minutes). The reaction was followed by thin layer chromatography (Kieselgel 60 F_{254}, E. Merck, ethyl acetate-benzene 1/9 as the eluant). After cooling to room temperature, crushed ice was added to the reaction mixture. The precipitated solid was filtered off, dried and then crystallized from a suitable solvent.

2-Nitro-3-aminobenzo[*b*]thiophene (**1a**).

This compound had mp 218-219° (from acetic acid) (lit [22] 218°).

2-Nitro-3-methylaminobenzo[*b*]thiophene (**1b**).

This compound had mp 200-202° (from dioxane).

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.83; H, 3.90; N, 13.37.

2-Nitro-3-propylaminobenzo[*b*]thiophene (**1c**).

This compound had mp 120-122° (from ethanol).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.11; N, 11.85. Found: C, 55.75; H, 5.09; N, 11.89.

2-Nitro-3-benzylaminobenzo[*b*]thiophene (**1d**).

This compound had mp 183-185° (from benzene).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.40; H, 4.23; N, 9.80.

General Procedure for the Preparation of Ethyl *N*-H and *N*-Alkyl-*N*-(2-nitrobenzo[*b*]thien-3-yl)oxalinates **2a-d**.

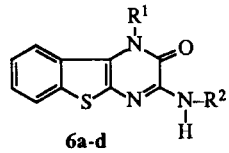
To a stirred solution of 2-nitro-3-aminobenzo[*b*]thiophenes **1a-d** (5 mmoles) in dioxane (100 ml) ethyl oxalyl chloride (15 mmoles) was added dropwise at room temperature. The reaction mixture was stirred for 12 hours and then poured into water. The separated solid was filtered off, dried and then crystallized from a suitable solvent. The yields, melting points, spectral and analytical data of compounds **2a-d** are gathered in Table 1.

General Procedure for the Preparation of Ethyl *N*-H and *N*-Alkyl-*N*-(2-aminobenzo[*b*]thien-3-yl)oxalinates **3a-d**.

A suspension of oxalinates **2a-d** (15 mmoles) in a 1:1 mixture of dioxane and water (20 ml) was heated until a clear solution was obtained. To this solution, kept at 50°, a hot sodium dithionite solution (60 mmoles in 50 ml of water) was added dropwise with stirring, and the reaction mixture was allowed to stand at 50° until the starting material was consumed (approximatively 10 minutes). The end of the reaction was monitored by thin layer chromatography (Kieselgel 60 F_{254}, E. Merck, benzene-ethyl

Table 4

1-Unsubstituted and 1-Alkyl-3-dialkylaminoalkylamino[1]benzothieno[2,3-*b*]pyriazin-2(1*H*)-ones **6a-d**



6a-d

Compound	R^1	R^2	Yield (%)	Mp (°C) (solvent)	Molecular Formula	M^+ (%)	Microanalytical Data (%) (Calcd./Found) C	H	N
6a	H	$(CH_2)_2N(CH_3)_2$	90	212-214 (EtOH)	$C_{14}H_{16}N_4OS$ (288.36)	288 (40)	58.31 58.24	5.59 5.51	19.42 19.12
6a	H	$(CH_2)_2$-morpholino	85	245-247 (MeOH)	$C_{17}H_{20}N_4OS$ (328.43)	328 (35)	62.17 62.39	6.13 6.05	17.05 16.95
6a	H	$(CH_2)_2$-morpholino	83	239-241 (EtOH)	$C_{16}H_{18}N_4O_2S$ (330.40)	330 (42)	58.16 57.94	5.49 5.29	16.95 16.80
6a	H	$(CH_2)_2$-pyrrolidino	80	211-213 (EtOH)	$C_{16}H_{18}N_4OS$ (314.40)	314 (37)	61.12 60.98	5.77 5.70	7.81 7.65
6a	H	$(CH_2)_3$-2-pyrrolidinone	87	221-223] (MeOH)	$C_{17}H_{18}N_4O_2S$ (342.41)	342 (43)	59.63 59.70	5.29 5.18	16.36 16.39
6b	CH_3	$(CH_2)_2N(CH_3)_2$	83	165-167 (Cyclohexane)	$C_{15}H_{18}N_4OS$ (302.39)	302 (40)	59.57 59.30	6.00 6.06	18.52 18.54
6b	CH_3	$(CH_2)_2$-piperidino	85	179-181 (Acetone)	$C_{18}H_{22}N_4OS$ (342.46)	342 (37)	63.13 63.07	6.47 6.50	16.36 16.50
6b	CH_3	$(CH_2)_2$-morpholino	80	209-211 (Acetone)	$C_{17}H_{20}N_4O_2S$ (344.43)	344 (45)	59.28 59.03	5.85 5.75	16.26 16.53
6b	CH_3	$(CH_2)_2$-pyrrolidino	81	168-170 (Acetone)	$C_{17}H_{20}N_4OS$ (328.43)	328 (38)	62.17 61.98	6.13 6.10	17.05 17.25
6b	CH_3	$(CH_2)_3$-2-pyrrolidinone	82	160-162 (Benzene)	$C_{18}H_{20}N_4O_2S$ (356.44)	356 (35)	60.65 60.54	5.65 5.59	15.71 15.75
6c	n-C_3H_7	$(CH_2)_2N(CH_3)_2$	76	173-175 (MeCN)	$C_{17}H_{22}N_4OS$ (330.44)	330 (25)	61.79 61.49	6.71 6.88	16.95 17.18
6c	n-C_3H_7	$(CH_2)_2$-piperidino	78	178-180 (Acetone)	$C_{20}H_{26}N_4OS$ (370.51)	370 (28)	64.83 64.70	7.07 7.15	15.12 15.26
6c	n-C_3H_7	$(CH_2)_2$-morpholino	80	185-187 (Acetone)	$C_{19}H_{24}N_4O_2S$ (372.48)	372 (30)	61.26 61.01	6.49 6.42	15.04 15.27
6c	n-C_3H_7	$(CH_2)_2$-pyrrolidino	84	168-170 (Acetone)	$C_{19}H_{24}N_4OS$ (356.48)	356 (40)	64.01 63.89	6.78 6.70	15.71 15.93
6c	n-C_3H_7	$(CH_2)_3$-2-pyrrolidinone	81	165-167 (Benzene)	$C_{20}H_{24}N_4O_2S$ (384.49)	384 (37)	62.47 62.85	6.29 6.24	14.57 14.85
6d	$CH_2C_6H_5$	$(CH_2)_2N(CH_3)_2$	85	218-220 (EtOH)	$C_{21}H_{22}N_4OS$ (378.49)	378 (35)	66.64 66.56	5.85 5.91	14.80 15.01
6d	$CH_2C_6H_5$	$(CH_2)_2$-piperidino	82	191-193 (Acetone)	$C_{24}H_{26}N_4OS$ (418.55)	418 (42)	68.87 68.63	6.26 6.19	13.38 13.54
6d	$CH_2C_6H_5$	$(CH_2)_2$-morpholino	85	202-204 (Acetone)	$C_{23}H_{24}N_4O_2S$ (420.53)	420 (35)	65.69 65.67	5.75 5.75	13.32 13.48
6d	$CH_2C_6H_5$	$(CH_2)_2$-pyrrolidino	82	188-190 (Acetone)	$C_{23}H_{24}N_4OS$ (404.53)	404 (37)	68.28 68.03	5.98 6.09	13.84 14.01
6d	$CH_2C_6H_5$	$(CH_2)_3$-2-pyrrolidinone	85	172-174 (MeOH)	$C_{24}H_{24}N_4O_2S$ (432.54)	432 (30)	66.64 66.49	5.59 5.57	12.95 12.78

acetate 1/1 as the eluant). After cooling, the separated precipitate was filtered off and the filtrate was extracted with ether (two portions of 25 ml). The extracts were washed with water, dried over anhydrous sodium sulfate and then evaporated to give a solid residue. The residue and precipitate were combined and crystallized from a suitable solvent. The yields, melting points, spectral and analytical data of compounds **3a-d** are given in Table 1.

General Procedure for the Preparation of 1*H* and 1-Alkyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-*b*]pyrazine-2,3-diones **4a-d**.

A solution of amino derivatives **3a-d** (20 mmoles) in glacial acetic acid (20 ml) was allowed to stir for 2 hours. The separated solid was filtered off and washed with ethanol to give a colourless powder of the dione. The yields, melting points, mass spectra and analytical data of diones **4a-d** are given in Table 2.

General Procedure for the Preparation of 1-Alkyl-3-chloro[1]-benzothieno[2,3-*b*]pyrazin-2(1*H*)-ones **5b-d**.

A solution of the 1-alkyldiones **4b-d** (20 mmoles) and thionyl chloride (27.5 mmoles) in toluene (50 ml) containing a 5% of *N*,*N*-dimethylformamide was refluxed at 120° for 1.5 hours and then filtered while hot to remove any insoluble material. The filtration was evaporated to dryness *in vacuo* and the residue was crystallized from a suitable solvent. The yields, melting points, mass spectra and analytical data of compounds **5b-d** are given in Table 2. The ^{1}H nmr data are given in Table 3.

3-Chloro[1]benzothieno[2,3-*b*]pyrazin-2(1*H*)-one (**5a**).

A solution of benzyl derivative **5d** (20 mmoles) in 96% sulfuric acid (5 ml) was stirred at room temperature for twenty minutes. The reaction mixture was slowly poured into crushed ice and then neutralized with sodium hydroxide. The resulting precipitate was filtered off, dried and then crystallized from ethanol. The yield, melting point, mass spectra and analytical data are included in Table 2. The ^{1}H nmr data are included in Table 3.

General Procedure for the Preparation of 1*H*- and 1-Alkyl-3-dialkylaminoalkylamino[1]benzothieno[2,3-*b*]pyrazin-2(1*H*)-ones **6a-d**.

A solution of 1*H*- or 1-alkyl-3-chloro derivatives **5a-d** (4 mmoles) and the appropriate dialkylaminoalkylamine (20 mmoles) in toluene (100 ml) was refluxed for 2 hours, until the starting chloro derivatives were consumed. The end of the reaction was monitored by thin layer chromatography (Kieselgel 60 F_{254}, E. Merck, ethyl acetate-methanol 1/1 as eluant). The solution was then evaporated to dryness *in vacuo* and the resulting residue was crystallized from a suitable solvent. The yields, melting points, mass spectra and analytical data are given in Table 4.

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