Pergamon

Tetrahedron 58 (2002) 8963–8972

TETRAHEDRON

Preparative and theoretical study on chain length-dependence and substrate selectivity in the cycloalkylation of condensed [1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thiones

Antal Csámpai,* Mónika Simó, Zoltán Szlávik, András Kotschy, Gábor Magyarfalvi and György Túrós

Institute of Chemistry, Eötvös Loránd University, P.O. Box 32, Budapest 112, H-1518, Hungary

Received 16 July 2002; revised 23 August 2002; accepted 12 September 2002

Abstract—Cyclization of condensed [1,2,4]triazolo[4,3-*b*]pyridazine-3(2*H*)-6(5*H*)-ones with α,ω-dibromoalkanes afforded a series of novel ring systems including zwitterions and isomeric tetracyclic lactams. The product distribution is controlled by the chain-length of the reagent, the polarity of the solvent and the structure of ring A in the substrate. The observed substrate selectivity was interpreted on the basis of amide-I IR frequencies and by the results of ab initio B3LYP DFT calculations carried out at 6-31G and 6-31G(d) basis sets using IPCM solvation model. The cycloalkylation with 1,4-dibromobutane gave also macrocyles as detectable by-products which underwent ring contraction yielding lactams on attempted chromatographic separation.

1. Introduction

In our previous paper[1] we reported on the ring transformation reactions of condensed [1,2,4]-triazolo[4,3-*b*] pyridazine-6(5*H*)-one-3(2*H*)-thiones **1a**–**e** (Scheme 1) effected by dialkyl acetylenedicarboxylates finally resulting in 3-carbamoylaryl-5,6-bis-methoxycarbo-nylthiazolo[2,3-*c*]-[1,2,4]triazoles **16a**–**e**. According to the proposed mechanism described in detail in Ref. 1 the transformation proceeds via the primarily formed tetracyclic 1,3,4-thiadiazines **2a**–**e** containing an active methyne group adjacent to the lactam moiety deprotonation of which is associated with ring enlargement of type **2**→**3**, the prerequisite of the subsequent elementary steps of the ring transformation. In order to get indirect evidence for the intermediacy of **2a**–**e** and to extend the group of novel polycondensed pyridazines of potential biological interest[2–5] we alkylated **1a**–**e** with *meso*-dimethyl-2,3-dibromosuccinate and α,ω-dibromoalkanes. The reactions were carried out in DMF in the presence of K_2CO_3 at 100°C and in refluxing $CHCl_3$–MeOH (5:1) containing Bu_4NOH as base, respectively (Methods A and B: Scheme 1).

2. Results and discussion

In keeping with the expectations based on the mechanism reported in Ref. 1 the reactions with *meso*-dimethyl-2,3-dibromosuccinate afforded **16a**–**e** by both the Methods used, but the yields were moderate (28–54%), as the transformations were accompanied by the formation of considerable amount of tarry substances in each case. The cycloalkylation of **1a**–**e** with 1,2-dibromoethane conducted under polar and less polar conditions (Methods A and B, Table 1) gave stable tetracyclic 1,3,4-thiadiazines **10a**–**e** (n=1) without activated C–H bonds in good yields (83–97%) indirectly supporting the view about the intermediacy of **2a**–**e** in the ring transformation process. Zwitterionic isomers **7a**–**e** containing two condensed five-membered rings were not formed even in trace amounts.

When 1,3-dibromopropane or 1,4-dibromobutane was applied as reagent, the direction of the transformations and the yields were found to be dependent both on the chain length and the polarity of the solvent used (Table 1). Conversions with 1,3-dibromopropane took place with much better yields as the reactions with 1,4-dibromobutane were accompanied by uncontrolled polymerization even in dilute solutions.

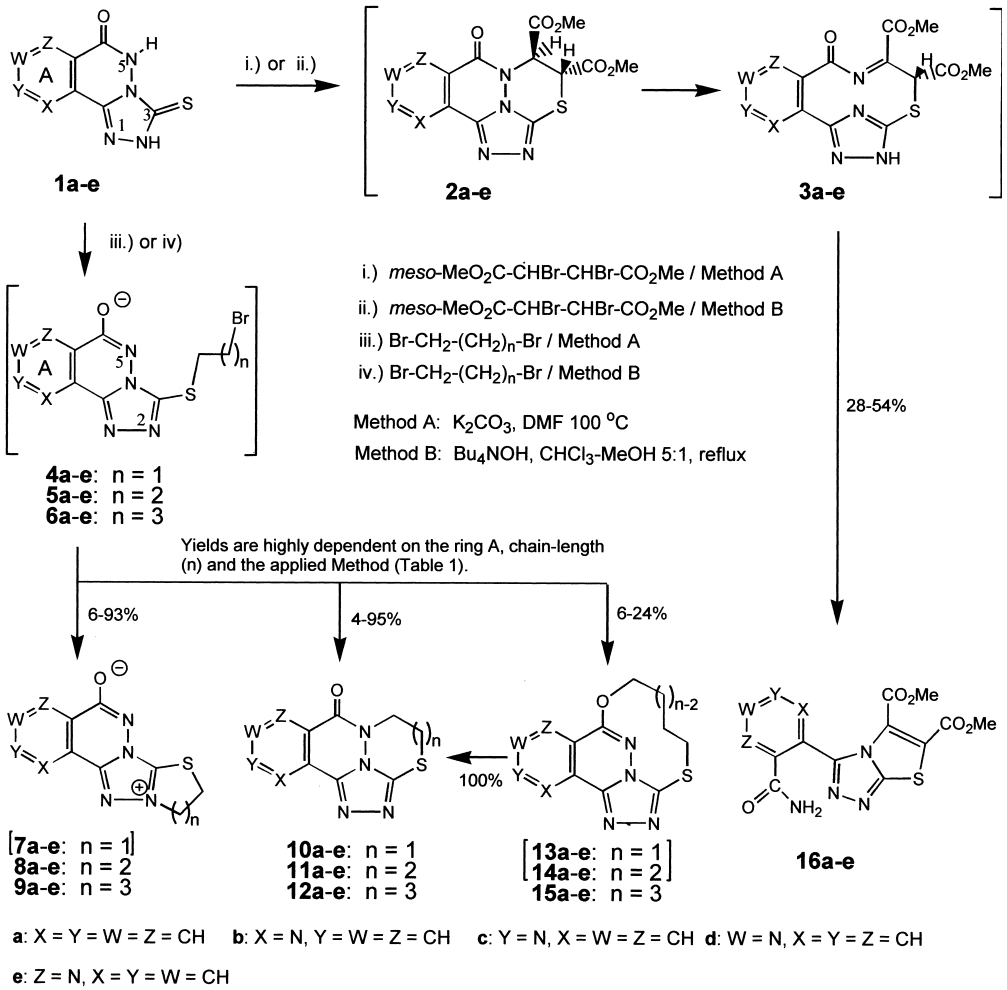
Reactions of **1a**,**c**,**d** with 1,3-dibromopropane in DMF (Method A) predominantly resulted in formation of isomeric tetracyclic 1,3,4-thiadiazepines **11a**,**c**,**d** and zwitterions **8a**,**c**,**d** in low yields (Table 1), while under the same conditions **1b**,**e** were almost exclusively converted into the poorly soluble zwitterionic 1,3-thiazines **8b**,**e** as major products (the yields for **11b** and **11e** were lower than 5%: Table 1).

For the reaction of **1b** with 1,3-dibromopropane conducted

Keywords: cyclisation; lactames; theoretical studies; zwitterions.

* Corresponding author. Tel.: +36-1-209-055x6591; fax: +36-1-209-0602; e-mail: csampai@para.chem.elte.hu

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01156-0



Scheme 1.

by Method B the product distribution was reversed relative to that obtained by Method A with the dominancy of condensed 1,3,4-thiadiazonine **11b** over zwitterionic **8b** (Table 1). Transformation of **1e** with 1,3-dibromopropane seemed to be much less sensitive to the change of the solvent giving again zwitterion **8e** as major product, although the yield of **11e** also became significant (Table 1). Analogous reactions of **1a**,**c**,**d** carried out by Method B resulted in the corresponding 1,3,4-thiadiazonines **11a**,**c**,**d** as exclusive products.

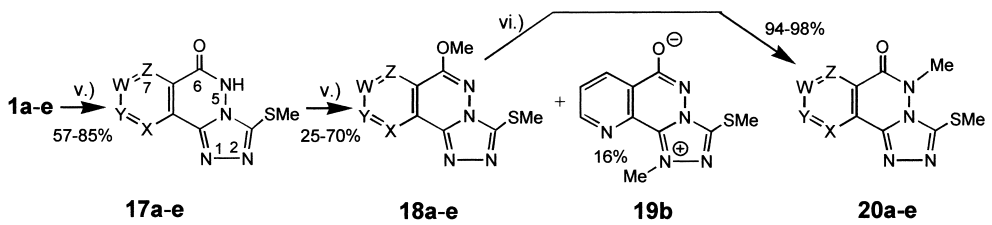
Table 1. Product distributions for reactions of **1a**–**e** with Br–$(CH_2)_n$–CH_2–Br in the dependence of the chain length (n) and the applied conditions (Method A/B)

	n	Detected yields[a] by Methods A/B			Separated yields[b] by Methods A/B	
1a	1		**10a** 89/94			**10a** 70/77
	2	**8a** 10/–	**11a** 76/89		**8a** 7/–	**11a** 64/74
	3	**9a** 17/7	**12a** 22/27	**15a** 18/24	**9a** 11/traces	**12a** 30/43
1b	1		**10b** 85/95			**10b** 73/87
	2	**8b** 93/37	**11b** 4/51		**8b** 87/28	**11b** –/40
	3	**9b** 27/10	**12b** 21/30	**15b** –/16	**9b** 22/6	**12b** 14/35
1c	1		**10c** 91/97			**10c** 82/84
	2	**8c** 14/–	**11c** 72/83		**8c** 9/–	**11c** 61/69
	3	**9c** 28/12	**12c** 24/30	**15c** –/19	**9c** 23/8	**12c** 16/42
1d	1		**10d** 95/92			**10d** 85/85
	2	**8d** 13/–	**11d** 81/87		**8d** 8/–	**11d** 71/69
	3	**9d** 21/6	**12d** 23/37	**15d** –/24	**9d** 16/traces	**12d** 13/45
1e	1		**10e** 83/86			**10e** 70/74
	2	**8e** 88/71	**11e** 5/21		**8e** 80/66	**11e** –/15
	3	**9e** 46/35	**12e** 11/14	**15e** –/6	**9e** 36/27	**12e** 7/15

[a] Obtained by taking simultaneously into account both the amount of the crude isolated mixture and its ^{1}H NMR analysis performed in DMSO-d_6.
[b] Referring to separated and purified compounds.

Interestingly, when 1,4-dibromobutane was applied as reagent by Method A, no pronounced selectivity was obtained for transformations **1a**–**d**→**9a**–**d**+**12a**–**d**, but a significant selectivity was again observable only in the transformation of **1e** giving zwitterionic **9e** as major product contaminated by 11% of condensed 1,3,4-thiadiazonine **12e** (Table 1). The reaction of benzo derivative **1a** with 1,4-dibromobutane also afforded a considerable amount (18%) of macrocyclic product **15a** containing a fused 1-oxa-3,4-diaza-6-thiacyclodecane ring which could only be identified by ^{1}H and ^{13}C NMR spectroscopy in the crude product also containing its isomers **9a** and **12a**.

Under the less polar conditions of Method B besides 1,3,4-thiadiazonines **12a**–**d**, the major products, significant amounts of macrocycles **15a**–**d** were also formed with 1,4-dibromobutane from compounds **1a**–**d**. Conversions **1e**→**12e** and **1e**→**15e** took place only in low detectable yields because formation of zwitterion **9e** was again the predominant process (Table 1). With shorter chains *S*,*O*-cycloalkylation producing **13a**–**e** or **14a**–**e** could not



Scheme 2. *Reaction conditions*: (v) MeI/Method A or Method B; (vi) silica/$CHCl_3$, 25°C.

Table 2. Proton affinity and charge distribution of the anions of **1a–e** using IPCM solvent model (dielectric constant=40)

Source of anion	Position of protonation	Proton affinity of anion (kcal mol^{-1})	Natural charge			
			O	*N*2	*N*5	*S*
1a	*N*2	289.54	−0.702	−0.443	0.049	−0.489
1a	*N*5	290.48	−0.791	0.064	−0.482	−0.403
1b	*N*2	290.11	−0.696	−0.425	0.062	−0.466
1b	*N*5	290.24	−0.788	0.071	−0.466	−0.389
1c	*N*2	289.28	−0.693	−0.432	0.062	−0.477
1c	*N*5	288.02	−0.787	0.066	−0.468	−0.393
1d	*N*2	286.91	−0.702	−0.426	0.054	−0.471
1d	*N*5	286.70	−0.789	0.067	−0.481	−0.393
1e	*N*2	285.77	−0.675	−0.441	0.042	−0.485
1e	*N*5	287.58	−0.755	0.061	−0.494	−0.402

be detected even in traces. During attempted chromatography over silica and alumina with a series of eluents (see Experimental) **15a–e** underwent ring contraction to give **12a–e**.

In order to get more insight into the nature of the studied cycloalkylation processes **1a–e** were also subjected to treatment with equimolar iodomethane (Scheme 2). Under both the applied conditions (Methods A and B) *S*-methylation occured to give selectively **17a–e** which, on subsequent treatment with the reagent, underwent *O*-methylation yielding **18a–e**. Methylation of **17b** performed in DMF (Method A) resulted in a 3:1 mixture of *S*,*O*-dimethyl derivative **18b** and zwitterionic *S*,*N*1-dimethyl derivative **19b**. On treatment with silica in chloroform *S*,*O*-dimethyl dervatives underwent O⟶N methyl-migration (**18⟶20**: Scheme 2) which is closely related to the above mentioned ring contraction of type **15⟶12**. It is also important to note that *O*-methylation of **17e** could only be achieved in low yields even by applying a great excess of the reagent (see Experimental).

Taking also the results of step-by-step alkylation experiments into account it can be concluded that in the course of the studied cyclizations, in keeping with the general expectations, bromoalkylation of the sulfur atom is the first step (**1⟶4–6**; Scheme 1) followed by ring closure to *N*2, *N*5 or, in the case of the bromobutyl chain only, to the carbonyl oxygen.

The primary alkylation of the sulfur atom was also supported by theoretical modelling. A convenient way to understand the reactivity of **1a–e** is to examine the spatial charge distribution and energetic data of these species via quantum mechanical calculations. Computations were performed using the Gaussian-98 program system.[6] Geometry optimizations of the neutral and deprotonated forms of these compounds were carried out using DFT with the 6-31G basis set and the hybrid Becke3LYP (B3LYP, Becke's three-parameter exchange[7] and Lee et al. correlation[8]) method based on density functional theory. To estimate relative N–H acidities at positions 2 and 5 of these molecules, the proton affinities of the corresponding anions were determined. Since the experiments were carried out in solvents we applied an adequate solvent model, IPCM,[9] built in the Gaussian program package. The basis set of these calculations was selected to optimize accuracy and computational costs: 6-31G for the hydrogen, 6-31G(d) for the carbon and 6-31+G(d) in case of the relevant nitrogen and sulfur atoms. The very similar proton affinity values of the *N*2 and *N*5-deprotonated pairs (Table 2) calculated with dielectric constant 40 (representing the conditions of Method A) clearly point to the corresponding neutral parent molecules having very similar acidity at these positions, so approximately the same amounts of the two anions must be present in the reaction mixtures.

The charge distribution of the parent molecules (Table 3) and their deprotonated forms (Table 2) were determined by natural bond orbital analysis (NBO) which is a more sophisticated partitioning method than the more often used Mulliken population analysis.[10] The computations (Tables 2 and 3) indicate that in **1a–e** the carbonyl oxygen is the most negatively charged atom and the electron density on the

Table 3. Total energy and charge distribution of **1a–e** using IPCM solvent model (dielectric constant=40)

	Energy (Hartree)	Natural charge			
		O	*N*2	*N*5	*S*
1a	−1039.003014	−0.671	0.085	0.050	−0.311
1b	−1055.040316	−0.631	0.095	0.064	−0.293
1c	−1055.036675	−0.620	0.092	0.063	−0.298
1d	−1055.036845	−0.674	0.092	0.054	−0.295
1e	−1055.034612	−0.642	0.083	0.041	−0.306

Table 4. Relative heats of formation of the corresponding isomerous pairs of compounds **7a–e–15a–e** calculated for dielectric constant 40 by B3LYP method at 6-31G basis set using IPCM solvation model (kcal mol^{-1})

	n=1		*n*=2		*n*=3	
	Δ*H*(**10–7**)	Δ*H*(**7–13**)	Δ*H*(**11–8**)	Δ*H*(**8–14**)	Δ*H*(**12–9**)	Δ*H*(**9–15**)
a	−17.08	−40.71	−0.82	−36.20	−2.01	−21.45
b	−20.75	−39.55	+0.66	−42.41	+0.87	−24.00
c	−20.13	−38.77	−3,34	−31.45	−5.54	−17.61
d	−23.73	−34.31	−5.02	−31.50	−6.78	−14.90
e	−18.14	−37.27	−0.02	−34.34	−1.74	−19.35

sulfur atom is much larger than that on *N*2 and *N*5 atoms. On the other hand, in both possible anions the deprotonated nitrogen carries a negative charge very close to the value found for the sulfur atom. However, it is noteworthy that a considerable increase of the negative charge (~0.1, cf. Tables 2 and 3) is induced on the sulfur atom even by *N*5-deprotonation which can be the consequence of their spatial close contact[11] made possible by their steric proximity (3.31–3.32 Å) revealed by geometry optimization. On the other hand, *N*2-deprotonation gives rise to a larger increase in the electron density on the sulfur (~0.18, cf. Tables 2 and 3) relative to that in the neutral molecule. It means that taking these charge distributions together with the expected effect of orbital control[12] into account in both deprotonated forms *S*-alkylation can take place as the preferred first step. The facile *S*-methylations presented in Scheme 2 are in agreement with this predicted selectivity. It is important to point out that primary *N*5- or *O*-alkylations with α,ω-dibromoalkanes would finally lead to the formation of lactames (**10–12**), while primary *N*2-alkylation would result in zwitterions (**7–9**).

Besides the straightforward and expected effect of the polarity of the solvent and the length of the bromoalkyl chain the structure of ring A has also a significant control over the direction of the cyclization of the primarily formed intermediates **4a–e–6a–e**. Since it was assumed that ring A basically influences the relative stability of the corresponding alternative ring systems we undertook again B3LYP calculations with geometry optimization at 6-31G level for three homologous groups of possible isomers (**7–10–13**, **8–11–14** and **9–12–15**; Scheme 1) followed by the calculation of their relative heats of formation in a solvent with dielectric constant 40 representing Method A, the condition in which the more pronounced selectivity originating from ring A was observed (Table 4).

These energy-calculations carried out at the same level of theory (B3LYP-6-31G) applying IPCM as solvation model spectacularly show that — in accord with the product distributions listed in Table 1 — formation of the strained condensed thiazoles **7a–e** (*n*=1) can practically be ruled out as the corresponding 1,3,4-thiadiazines **10a–e** are much more stable independently on ring A while the relative heats of formation obtained for the homologous isomeric pairs **11a–d/8a–d** (*n*=2) and **12a–d/9a–d** (*n*=3) suggest that intramolecular *N*2-alkylation in the *S*-bromopropyl- and bromobutyl intermediates (**5→8** and **6→9**) can successfully compete with the alternative *N*5- or *O*-alkylation steps (**5→11** and **6→12** or **6→15**; Scheme 1). Moreover, the tendency of these data are in good accord with the 'ring A-dependent' product distributions detected for the reactions with 1,3-dibromopropane which are obviously controlled by the relative stability of the corresponding isomeric pairs **8/11** as **8b,e** proved to be of enhanced stability. On the other hand, in spite of the similar relative stability of homologous zwitterions **8b,e** and **9b,e**, the formation of the latter is less favoured probably due to intramolecular *O*-alkylation followed by ring contraction (**6→15→12**; Scheme 1) yielding significant amounts of macrocycles **15b,e**. In general, the increased amounts of condensed 1,2,4-thiadiazocines **12a–e** in the crude reaction mixtures can be ascribed to this pathway which is accessible only for the bromobutylthio intermediates **6a–e**. Analogous *O*-alkylations in **4a–e** and **5a–e** are sterically disfavoured processes as they would result in strained ring systems **13a–e** and **14a–e**, respectively (Scheme 1). This view is firmly supported by the comparison of the relative heats of formation for isomeric pairs **10a–e/13a–e** (*n*=1), **11a–e/14a–e** (*n*=2) and **12a–e/15a–e** (*n*=3) listed in Table 4. The results spectacularly indicate that **15a–e** are sterically the least strained ring systems among the *S*,*O*-cycloalkylated molecules having some chance to develop probably under kinetic control in both the solvents used.

Finally it is worth noting that pyridine (ring A) when fused with [2,3-*g*] mode to the triazolopyridazinone system (intermediates **5e** and **6e**) retards most markedly ring closure to the amidate moiety (*N*5 and *O* atoms) simultaneously allowing the formation of significant amounts of the corresponding zwitterions (**8e**, **9e**). This tendency cannot be explained alone on the basis of the thermodynamic data obtained for isomeric pairs **11e/8e** (*n*=2) and **12e/9e** (*n*=3) but can at least partly be ascribed to the strong electron-withdrawing effect exerted by the adjacent pyridine nitrogen on the amidate part. The same effect of this ring junction is reflected in the above mentioned sluggish *O*-methylation of *S*-methyl derivative **17e** (Scheme 2) and from the comparison of the amide-I IR-frequencies of **10a–e**. The highest frequency was measured for **10e** and similar tendency is observable for the amide-I bands of **11a–e** and **12a–e** also showing that the conjugation in the lactam moiety is decreased with the

Table 5. Amide-I IR-frequencies (cm^{-1}) measured in KBr pellet for lactams **10–12**

	a	**b**	**c**	**d**	**e**
10	1657	1659	1669	1668	1685
11	1664	1675	1680	1683	1698
12	1670	1684	1687	1687	1704

increasing size of the condensed ring associated with the increasing pyramidal character of the *N*5 atom (Table 5). Concluding from the theoretical modelling and the IR data it can be established that in the course of cyclization of the assumed bromoethylthio intermediate **4e** (Scheme 1) exclusively *N*5-alkylation can construct a ring system (**10e**) without any significant internal strain which obviously overcompensates the effect of the decreased nucleophilicity of the amidate moiety.

The structure determination of the products was straightforward by IR, ^{1}H and ^{13}C NMR spectroscopy including 2D-COSY, HSQC and HMBC (data are listed in Table 5 and Experimental). Only the following important notes are necessary: (i) no amide-I band is discernible in the IR spectra of zwitterions **8a–e**, **9a–e**, **19b**; (ii) in the 2D-HMBC spectra of zwitterions **8a–e** and **9a–e** both *S*–CH_2 and *N*2–CH_2 protons are correlated to the C3 atom, while in the 2D-HMBC spectra of tetracyclic lactames **10a–e**–**12a–e** *S*–CH_2 and *N*5–CH_2 protons exhibit cross peaks with C3 and C6-atoms, respectively (this numbering of atoms concerns to the system applied to **1a–e**); (iii) macrocycles **15a–e** were identified in the crude reaction mixtures on the basis of their 2D-COSY, HSQC and HMBC spectra taken after assignment of the characteristic downfield-shifted *O*–CH_2 carbon line (67.2–67.5 ppm).

3. Conclusion

The facile ring closure of condensed [1,2,4]triazolo[4,3-*b*]-pyridazinone-3(2*H*)-thione-6(5*H*)-ones **1a–e** effected by α,ω-dibromoalkanes results in easily separable lactams (**10a–e**–**12a–e**) and zwitterions (**8a–e** and **9a–e**) representing a series of novel heterocyclic systems of various ring size and potential biological interest. According to supplementary preparative experiments and quantum mechanical modelling *S*-bromoalkylation is the primary step in the course of the cyclizations studied. The product distribution can obviously be influenced by the polarity of the solvent used and on the chain-length of the reagent. Ring A also has a significant effect on the direction of the ring closure in the assumed bromopropylthio- and bromobutylthio intermediates **5a–e** and **6a–e** (Scheme 1). The nature of this unusual 'remote control' by ring A lies in the theoretically established tendency that zwitterions incorporating pyrido[2,3-*d*]- or pyrido[3,2-*d*]pyridazine subunit (**8b**,**e** and **9b**,**e**) are of enhanced stability relative to their analogues incorporating phthalazine-, pyrido[3,4-*d*]- or pyrido[4,3-*d*]pyridazine subunit (**8a**,**c**,**d** and **9a**,**c**,**d**). On the other hand, ring closure of bromobutylthio intermediates **6a–e** can also take place on the negatively polarized carbonyl oxygen affording metastable macrocycles **15a–e** which easily undergo ring contraction to give condensed thiadiazocines **12a–e** under the conditions of column chromatography.

4. Experimental

Melting points (uncorrected) were determined with a Boetius microstage. The IR spectra were recorded in KBr pellets with a BRUKER IFS 55 FT-spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution (except for **18a–e** and **20a–e** which were measured in $CDCl_3$) in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C), with the deuterium signal of the solvent as the lock and TMS as internal reference. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. The 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively. The assignment of the ^{1}H NMR signals of ring A given for each of the compounds described below refers to the numbering of atoms applied to **1a–e** (see: Scheme 1).

4.1. General procedures for alkylation with α,ω-dibromoalkanes

Method A. The corresponding thione **1a–e** (2 mmol) and K_2CO_3 (0.498 g, 4 mmol) were dissolved in dry DMF (25 mL) by stirring and gentle heating under argon. The corresponding α,ω-dibromoalkane (2 mmol) was added to the clear yellow solution which was then kept at 100°C for 2 h. After evaporation of the solvent in vacuo the brown residue (solid or oily) was trituated with water (10–15 mL) to obtain the crude solid product (white or pale yellow) of which composition (Table 1) was analysed by ^{1}H NMR. The purification of **10a–e** and **16a–e** was performed by recrystallization from ethanol. The separation of isomeric pairs of types **8/11** and **9/12** was carried out by column chromatography over silica. Lactams **11a–e** and **12a–e** were eluted by $CHCl_3$–MeOH 5:1. Zwitterions **8a–e** and **9a–e** were removed from the silica by MeOH. The separated **11a–e** and **12a–e** were recrystallized from ethanol, **8a–e** and **9a–e** were further purified by recrystallization from different mixtures (~1:3–2:3) of DMF–ethanol.

Method B. The corresponding thione **1a–e** (2 mmol) was suspended in $CHCl_3$ (20 mL) under argon. To this suspension 1 M methanolic solution of Bu_4NOH (4 mL) was added and stirred for 20 min. After this period 2 mmol of the corresponding α,ω-dibromoalkane (2 mmol) was added and the resulting mixture was refluxed for 2 h. The work-up of the reaction mixture and the separation and purification of the products were carried out as described in Method A. Yields are listed in Table 1. Separation of the mixtures of lactams **12a–e** and their macrocyclic isomers **15a–e** was attempted both on silica (Merck grade 9385, 230–400 mesh, 60 Å) and alumina (neutral, Brockmann I, ~150 mesh, 58 Å) by elution with the following mixtures: $CHCl_3$–MeOH 5:1; $CHCl_3$–MeOH 10:1; $CHCl_3$–EtOAc 3:1; CH_2Cl_2–EtOAc 3:1; CH_2Cl_2–EtOAc 5:1; *n*-hexane–EtOAc 2:1, however, after evaporation of the eluent exclusively **12a–e** were isolated in pure form. Compounds **15a–e** were identified in the primarily isolated mixtures of solid substances by ^{1}H and ^{13}C NMR spectroscopy. The assignments listed below are based on 2D-COSY, HSQC and HMBC measurements.

Yields (% by Method A/B) for thiazolo[2,3-*c*][1,2,4]triazoles: **16a** 35/54; **16b** 46/51; **16c** 28/39; **16d** 32/38; **16e** 37/48. Description of **16a–e** is reported in Ref. 1.

4.1.1. 3,4-Dihydro-2*H*-[1,3]thiazino[2′,3′:5,1][1,2,4]triazolo[3,4-*a*]phthalazine-5-ium-10b-olate (8a). White powder; mp 294–297°C; ν_{max} 1582, 1538 cm^{-1}; δ_H 8.23 (1H, m, H7), 8.16 (1H, m, H10), 7.84 (2H, m, H8 and H9), 4.49 (2H, t, *J*=5.5 Hz, NCH_2), 3.48 (2H, t, *J*=5.5 Hz, SCH_2), 2.49 (2H, quin, *J*=5.5 Hz, CCH_2C); δ_C 164.7, 141.7, 140.2, 133.1, 132.5, 128.9, 128.2, 123.1, 121.7, 52.9, 30.0, 27.5; Anal. calcd for $C_{12}H_{10}N_4OS$ (258.31) C 55.80, H 3.90, N 21.69, S 12.41; Found C 55.77, H 3.86, N 21.75, S 12.39%.

4.1.2. 3,4,-Dihydro-2*H*-pyrido[2,3-*d*][1,3]thiazino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-5-ium-10b-olate (8b). Yellow needless; mp 311–314°C; ν_{max} 1605, 1579, 1543 cm^{-1}; δ_H 9.00 (1H, dd, *J*=4.6, 1.8 Hz, H9), 8.54 (1H, dd, *J*=7.8, 1.8 Hz, H7), 7.85 (1H, dd, *J*=7.8, 4.6 Hz, H8), 4.48 (2H, t, *J*=5.5 Hz, NCH_2), 3.48 (2H, t, *J*=5.5 Hz, SCH_2), 2.48 (2H, quin, *J*=5.5 Hz, CCH_2C); δ_C 164.9, 155.1, 141.1, 140.4, 140.2, 137.0, 128.1, 125.6, 52.9, 30.0, 27.4; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 51.01, H 3.57, N 26.99, S 12.40%.

4.1.3. 3,4,-Dihydro-2*H*-pyrido[3,4-*d*][1,3]thiazino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-5-ium-10b-olate (8c). Pale yellow needless; mp 319–323°C; ν_{max} 1601, 1582, 1548 cm^{-1}; δ_H 9.41 (1H, s, H10), 8.93 (1H, d, *J*=5.0 Hz, H8), 8.15 (1H, d, *J*=5.0 Hz, H7), 4.48 (2H, t, *J*=5.5 Hz, NCH_2), 3.48 (2H, t, *J*=5.5 Hz, SCH_2), 2.47 (2H, quin, *J*=5.5 Hz, CCH_2C); δ_C 165.3, 151.9, 146.3, 140.6, 140.0, 130.5, 123.2, 119.1, 52.9, 30.0, 27.5; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.91, H 3.59, N 26.96, S 12.42%.

4.1.4. 3,4,-Dihydro-2*H*-pyrido[4,3-*d*][1,3]thiazino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-5-ium-10b-olate (8d). White powder; mp 323–326°C; ν_{max} 1603, 1580, 1547 cm^{-1}; δ_H 9.31 (1H, s, H7), 8.97 (1H, d, *J*=5.0 Hz, H9), 8.10 (1H, d, *J*=5.0 Hz, H10), 4.49 (2H, t, *J*=5.5 Hz, NCH_2), 3.48 (2H, t, *J*=5.5 Hz, SCH_2), 2.47 (2H, quin, *J*=5.5 Hz, CCH_2C); δ_C 165.0, 154.0, 150.7, 142.1, 140.2, 131.3, 122.1, 116.5, 52.9, 30.0, 27.4; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.88, H 3.54, N 27.08, S 12.36%.

4.1.5. 3,4,-Dihydro-2*H*-pyrido[3,2-*d*][1,3]thiazino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-5-ium-10b-olate (8e). Grey powder; mp 306–310°C; ν_{max} 1599, 1577, 1547 cm^{-1}; δ_H 9.09 (1H, dd, *J*=4.9, 1.5 Hz, H8), 8.58 (1H, dd, *J*=7.8, 1.5 Hz, H7), 7.83 (1H, dd, *J*=7.8, 4.9 Hz, H9), 4.46 (2H, t, *J*=5.5 Hz, NCH_2), 3.47 (2H, t, *J*=5.5 Hz, SCH_2), 2.46 (2H, quin, *J*=5.5 Hz, CCH_2C); δ_C 163.7, 155.3, 144.2, 140.7, 140.0, 132.5, 127.5, 121.7, 52.7, 29.8, 27.5; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.92, H 3.56, N 27.05, S 12.34%.

4.1.6. 2,3,4,5-Tetrahydro[1,3]thiazepino[2′,3′:5,1]-[1,2,4]triazolo[3,4-*a*]phthalazine-6-ium-11b-olate (9a). White powder; mp 282–285°C; ν_{max} 1600, 1586, 1541 cm^{-1}; δ_H 8.25 (1H, m, H7), 8.14 (1H, m, H10), 7.83 (2H, m, H8 and H9), 4.66 (2H, t, *J*=5.1 Hz, NCH_2), 3.28 (2H, t, *J*=5.1 Hz, SCH_2), 2.21 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$), 2.00 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 165.0, 141.6, 141.5, 133.0, 132.4, 128.6, 128.4, 122.9, 122.0, 55.2, 33.0, 31.4, 25.3; Anal. calcd for $C_{13}H_{12}N_4OS$ (272.33) C 57.34, H 4.44, N 20.57, S 11.77; Found C 57.39, H 4.38, N 20.52, S 11.80%.

4.1.7. 2,3,4,5-Tetrahydropyrido[2,3-*d*][1,3]thiazepino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-6-ium-11b-olate (9b). Grey powder; mp 300–304°C; ν_{max} 1602, 1576, 1548 cm^{-1}; δ_H 9.03 (1H, dd, *J*=4.5, 1.8 Hz, H9), 8.51 (1H, dd, *J*=7.8, 1.8 Hz, H7), 7.87 (1H, dd, *J*=7.8, 4.5 Hz, H8), 4.66 (2H, t, *J*=5.1 Hz, NCH_2), 3.28 (2H, t, *J*=5.1 Hz, SCH_2), 2.21 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$), 2.00 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 164.3, 155.6, 141.1, 140.9, 140.0, 137.2, 127.8, 125.4, 55.1, 33.0, 31.3, 25.3; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.82, H 4.00, N 25.67, S 11.71%.

4.1.8. 2,3,4,5-Tetrahydropyrido[3,4-*d*][1,3]thiazepino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-6-ium-11b-olate (9c). Yellowish powder; mp 308–312°C; ν_{max} 1607, 1574, 1547 cm^{-1}; δ_H 9.46 (1H, s, H10), 8.91 (1H, d, *J*=5.0 Hz, H8), 8.20 (1H, d, *J*=5.0 Hz, H7), 4.67 (2H, t, *J*=5.1 Hz, NCH_2), 3.29 (2H, t, *J*=5.1 Hz, SCH_2), 2.21 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$), 1.99 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 166.3, 152.1, 146.6, 141.2, 140.3, 130.2, 123.0, 118.4, 55.4, 33.1, 31.3, 25.3; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.74, H 4.10, N 25.56, S 11.80%.

4.1.9. 2,3,4,5-Tetrahydropyrido[4,3-*d*][1,3]thiazepino [2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-6-ium-11b-olate (9d). Yellowish powder; mp 310–314°C; ν_{max} 1604, 1579, 1550 cm^{-1}; δ_H 9.36 (1H, s H7), 8.91 (1H, d, *J*=5.0 Hz, H9), 8.20 (1H, d, *J*=5.0 Hz, H10), 4.66 (2H, t, *J*=5.1 Hz, NCH_2), 3.28 (2H, t, *J*=5.1 Hz, SCH_2), 2.21 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$), 2.00 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 164.7, 154.7, 151.5, 142.4, 149.6, 130.7, 122.0, 116.8, 55.3, 33.0, 31.6, 25.3; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.80, H 4.12, N 25.69, S 11.82%.

4.1.10. 2,3,4,5-Tetrahydropyrido[3,2-*d*][1,3]thiazepino-[2′,3′:5,1][1,2,4]triazolo[4,3-*b*]pyridazine-6-ium-11b-olate (9e). Yellowish needless; mp 293–297°C; ν_{max} 1603, 1572, 1548 cm^{-1}; δ_H 9.12 (1H, dd, *J*=5.0, 1.6 Hz, H8), 8.60 (1H, dd, *J*=7.8, 1.6 Hz, H10), 7.80 (1H, dd, *J*=7.8, 5.0 Hz, H9), 4.66 (2H, t, *J*=5.1 Hz, NCH_2), 3.28 (2H, t, *J*=5.1 Hz, SCH_2), 2.21 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$), 2.00 (2H, quin, *J*=5.1 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 164.1, 155.0, 144.5, 141.1, 140.3, 133.0, 127.1, 121.4, 55.2, 33.0, 31.4, 25.4; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.63, H 4.15, N 25.62, S 11.77%.

4.1.11. 4,5-Dihydro[1,3,4]thiadiazino[2,3,4-*cd*]-[1,2,4]-triazolo[3,4-*a*]phthalazine 7(6*H*)-one (10a). White powder; mp 163–165°C; ν_{max} 1657, 1574, 1540 cm^{-1}; δ_H 8.27 (1H, d, *J*=7.6 Hz, H7), 8.25 (1H, d, *J*=7.6 Hz, H10), 7.95 (1H, t, *J*=7.6 Hz, H9), 7.80 (1H, t, *J*=7.6 Hz, H8), 4.53 (2H, t, *J*=5.2 Hz, NCH_2), 3.52 (2H, t, *J*=5.2 Hz, SCH_2); δ_C 157.3, 142.3, 138.5, 135.3, 131.7, 131.6, 129.1, 124.1, 123.2, 42.8, 23.3; Anal. calcd for $C_{11}H_8N_4OS$ (244.28) C 54.09, H 3.30,

N 22.94, S 13.13; Found C 54.01, H 3.37, N 23.02, S 13.13%.

4.1.12. 4,5-Dihydropyrido[3,2-*g*][1,3,4]thiadiazino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-7(6*H*)-one (10b). White powder; mp 177–180°C; ν_{max} 1659, 1587, 1532 cm^{-1}; δ_H 9.09 (1H, dd, *J*=4.3, 1.6 Hz, H9), 8.59 (1H, dd, *J*=7.9, 1.6 Hz, H7), 7.82 (1H, dd, *J*=7.9, 4.3 Hz, H8), 4.54 (2H, t, *J*=5.2 Hz, NCH_2), 3.53 (2H, t, *J*=5.2 Hz, SCH_2); δ_C 157.5, 156.0, 143.1, 142.1, 139.2, 137.4, 126.5, 121.4 43.1, 23.2; Anal. calcd for $C_{10}H_7N_5OS$ (245.27) C 48.97, H 2.88, N 28.55, S 13.07; Found C 49.01, H 2.82, N 28.71, S 13.12%.

4.1.13. 4,5-Dihydropyrido[4,3-*g*][1,3,4]thiadiazino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-7(6*H*)-one (10c). Pale yellowish powder; mp 172–174°C; ν_{max} 1669, 1578, 1538 cm^{-1}; δ_H 9.56 (1H, s, H10), 8.99 (1H, d, *J*=4.9 Hz, H8), 8.11 (1H, d, *J*=4.9 Hz, H7), 4.53 (2H, t, *J*=5.2 Hz, NCH_2), 3.52 (2H, t, *J*=5.2 Hz, SCH_2); δ_C 157.2, 152.8, 145.4, 140.6, 139.2, 130.1, 122.4, 118.8, 42.9, 23.2; Anal. calcd for $C_{10}H_7N_5OS$ (245.27) C 48.97, H 2.88, N 28.55, S 13.07; Found C 48.88, H, 2.92, N 28.60, S 13.10%.

4.1.14. 4,5-Dihydropyrido[3,4-*g*][1,3,4]thiadiazino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-7(6*H*)-one (10d). White powder; mp 181–184°C; ν_{max} 1668, 1608 cm^{-1}; δ_H 9.36 (1H, s, H7), 9.02 (1H, d, *J*=5.1 Hz, H9), 8.14 (1H, d, *J*=5.1 Hz, H10), 4.51 (2H, t, *J*=5.1 Hz, NCH_2), 3.52 (2H, t, *J*=5.1 Hz, SCH_2); δ_C 156.7, 154.8, 151.1, 141.0, 140.0, 130.3, 118.7, 116.1, 42.8, 23.3; Anal. calcd for $C_{10}H_7N_5OS$ (245.27) C 48.97, H 2.88, N 28.55, S 13.07; Found C 48.90, H 2.85, N 28.71, S 13.11%.

4.1.15. 4,5-Dihydropyrido[2,3-*g*][1,3,4]thiadiazino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-7(6*H*)-one (10e). Pale grey powder; mp 184–186°C; ν_{max} 1685, 1599, 1543 cm^{-1}; δ_H 9.01 (1H, dd, *J*=4.5, 1.5 Hz, H8), 8.67 (1H, dd, *J*=8.0, 1.5 Hz, H10), 7.93 (1H, dd, *J*=8.0, 4.5 Hz, H9), 4.55 (2H, t, *J*=5.1 Hz, NCH_2), 3.54 (2H, t, *J*=5.1 Hz, SCH_2); δ_C 155.8, 153.0, 141.7, 140.6, 138.8, 131.7, 129.2, 121.6, 43.1, 23.5; Anal. calcd for $C_{10}H_7N_5OS$ (245.27) C 48.97, H 2.88, N 28.55, S 13.07; Found C 49.05, H 2.81, N 28.62, S 13.08%.

4.1.16. 5,6-Dihydro-4*H*-[1,3,4]thiadiazepino[2,3,4-*cd*]-[1,2,4]triazolo[3,4-*a*]phthalazine-8(7*H*)-one (11a). White powder; mp 150–152°C; ν_{max} 1664, 1589, 1540 cm^{-1}; δ_H 8.23 (1H, d, *J*=7.8 Hz, H7), 8.21 (1H, d, *J*=7.8 Hz, H10), 7.92 (1H, t, *J*=7.8 Hz, H9), 7.78 (1H, t, *J*=7.8 Hz, H8), 4.76 (2H, t, *J*=6.0 Hz, CH_2), 3.53 (2H, t, *J*=6.0 Hz, SCH_2), 2.26 (2H, quin, *J*=6.0 Hz, CCH_2C); δ_C 159.6, 144.1, 143.7, 135.2, 131.7, 129.2, 125.0, 124.8, 123.2, 47.0, 31.4, 28.7; Anal. calcd for $C_{12}H_{10}N_4OS$ (258.31) C 55.80, H 3.90, N 21.69, S 12.41; Found C 55.82, H 3.84, N 21.59, S 12.36%.

4.1.17. 5,6-Dihydro-4*H*-pyrido[3,2-*g*][1,3,4]thiadiazepino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-8(7*H*)-one (11b). White powder; mp 155–157°C; ν_{max} 1675, 1591, 1546 cm^{-1}; δ_H 9.07 (1H, dd, *J*=4.2, 1.6 Hz, H9), 8.60 (1H, dd, *J*=7.9, 1.6 Hz, H7), 7.80 (1H, dd, *J*=7.9, 4.2 Hz, H8), 4.75 (2H, t, *J*=6.0 Hz, NCH_2), 3.52 (2H, t, *J*=6.0 Hz, SCH_2), 2.27 (2H, quin, *J*=6.0 Hz, CCH_2C); δ_C 159.5, 156.0, 144.0, 143.3, 140.0, 138.5, 125.7, 121.8, 47.1, 31.5, 28.6; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.91, H 3.61, N 26.92, S 12.36%.

4.1.18. 5,6-Dihydro-4*H*-pyrido[4,3-*g*][1,3,4]thiadiazepino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-8(7*H*)-one (11c). Pale yellowish powder; mp 161–164°C; ν_{max} 1680, 1595, 1550 cm^{-1}; δ_H 9.47 (1H, s, H10), 8.95 (1H, d, *J*=5.0 Hz, H8), 8.04 (1H, d, *J*=5.0 Hz, H7), 4.73 (2H, t, *J*=6.0 Hz, NCH_2), 3.52 (2H, t, *J*=6.0 Hz, SCH_2), 2.25 (2H, quin, *J*=6.0 Hz, CCH_2C); δ_C 158.5, 152.1, 145.6, 144.3, 142.5, 131.0, 121.4, 119.8, 47.3, 31.4, 28.4; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.90, H 3.57, N 27.10, S 12.47%.

4.1.19. 5,6-Dihydro-4*H*-pyrido[3,4-*g*][1,3,4]thiadiazepino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-8(7*H*)-one (11d). Yellowish powder; mp 149–151°C; ν_{max} 1683, 1606, 1542 cm^{-1}; δ_H 9.31 (1H, s, H7), 8.99 (1H, d, *J*=5.0 Hz, H9), 8.09 (1H, d, *J*=5.0 Hz, H10), 4.73 (2H, t, *J*=6.0 Hz, NCH_2), 3.52 (2H, t, *J*=6.0 Hz, SCH_2), 2.25 (2H, quin, *J*=6.0 Hz, CCH_2C); δ_C 159.0, 154.0, 151.0, 145.0, 142.9, 131.2, 119.5, 116.1, 47.2, 31.4, 28.5; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.93, H 3.60, N 27.04, S 12.35%.

4.1.20. 5,6-Dihydro-4*H*-pyrido[2,3-*g*][1,3,4]thiadiazepino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-8(7*H*)-one (11e). Yellowish powder; mp 153–156°C; ν_{max} 1698, 1598, 1537 cm^{-1}; δ_H 9.03 (1H, dd, *J*=4.5, 1.5 Hz, H8), 8.70 (1H, dd, *J*=8.0, 1.5 Hz, H10), 7.94 (1H, dd, *J*=8.0, 4.5 Hz, H9), 4.73 (2H, t, *J*=6.0 Hz, NCH_2), 3.52 (2H, t, *J*=6.0 Hz, SCH_2), 2.25 (2H, quin, *J*=6.0 Hz, CCH_2C); δ_C 157.4, 153.2, 145.8, 142.8, 140.1, 132.2, 129.8, 121.9, 47.2, 31.5, 28.5; Anal. calcd for $C_{11}H_9N_5OS$ (259.29) C 50.95, H 3.50, N 27.01, S 12.37; Found C 50.88, H 3.55, N 26.96, S 12.33%.

4.1.21. 4,5,6,7-Tetrahydro[1,3,4]thiadiazocino[2,3,4-*cd*]-[1,2,4]triazolo[3,4-*a*]phthalazine-9(8*H*)-one (12a). White needless; mp 134–137°C; ν_{max} 1670, 1601, 1546 cm^{-1}; δ_H 8.36 (1H, d, *J*=7.8 Hz, H7), 8.26 (1H, d, *J*=7.8 Hz, H10), 7.98 (1H, t, *J*=7.8 Hz, H9), 7.87 (1H, t, *J*=7.8 Hz, H8), 5.20 (2H, t, *J*=6.0 Hz, NCH_2), 3.18 (2H, t, *J*=6.0 Hz, SCH_2), 2.13 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$), 1.81 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 158.2, 145.0, 140.2, 135.2, 132.1, 128.9, 124.6, 124.5, 123.5, 43.6, 36.3, 29.1, 23.6; Anal. calcd for $C_{13}H_{12}N_4OS$ (272.33) C 57.34, H 4.44, N 20.57, S 11.77; Found C 57.40, H 4.51, N 20.52, S 11.79%.

4.1.22. 4,5,6,7-Tetrahydropyrido[3,2-*g*][1,2,4]thiadiazocino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-9(8*H*)-one (12b). Grey powder; mp 139–142°C; ν_{max} 1684, 1604, 1547 cm^{-1}; δ_H 8.91 (1H, dd, *J*=4.2, 1.6 Hz, H9), 8.64 (1H, dd, *J*=7.9, 1.6 Hz, H7), 7.80 (1H, dd, *J*=7.9, 4.2 Hz, H8), 5.20 (2H, t, *J*=6.0 Hz, NCH_2), 3.19 (2H, t, *J*=6.0 Hz, SCH_2), 2.11 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$), 1.82 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 159.7, 156.1, 144.0, 143.8, 140.0, 137.9, 125.0, 121.2, 43.6, 36.2, 29.0, 23.6; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.77, H 3.98, N 25.69, S 11.77%.

4.1.23. 4,5,6,7-Tetrahydropyrido[4,3-*g*][1,2,4]thiadiazocino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-9(8*H*)-one (12c). Yellowish powder; mp 131–132°C; ν_{max} 1687, 1597, 1551 cm^{-1}; δ_H 9.40 (1H,s, H10), 8.92 (1H, d, *J*= 5.0 Hz, H8), 8.00 (1H, d, *J*=5.0 Hz, H7), 5.21 (2H, t, *J*= 6.0 Hz, NCH_2), 3.19 (2H, t, *J*=6.0 Hz, SCH_2), 2.11 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$), 1.82 (2H, quin, *J*= 5.9 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 160.2, 151.8, 145.8, 142.5, 140.4, 131,6, 120.4, 112.2, 43.5, 36.2, 29.3, 23.6; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.80, H 4.10, N 25.56, S 11.70%.

4.1.24. 4,5,6,7-Tetrahydropyrido[3,4-*g*][1,2,4]thiadiazocino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-9(8*H*)-one (12d). Yellowish powder; mp 128–129°C; ν_{max} 1687, 1599, 1539 cm^{-1}; δ_H 9.37 (1H,s, H7), 8.94 (1H, d, *J*= 5.0 Hz, H8), 8.02 (1H, d, *J*=4.9 Hz, H10), 5.20 (2H, t, *J*= 6.0 Hz, NCH_2), 3.19 (2H, t, *J*=6.0 Hz, SCH_2), 2.12 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$), 1.81 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 159.8, 154.1, 150.6, 144.7, 140.4, 132.1, 119.3, 116.4, 43.6, 36.3, 29.3, 23.6; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.82, H 4.02, N 25.59, S 11.72%.

4.1.25. 4,5,6,7-Tetrahydropyrido[2,3-*g*][1,2,4]thiadiazocino[2,3,4-*cd*]-[1,2,4]triazolo[4,3-*b*]pyridazine-9(8*H*)-one (12e). Yellow needless; mp 137–139°C; ν_{max} 1704, 1601, 1535 cm^{-1}; δ_H 9.00 (1H, dd, *J*=4.4, 1.5 Hz, H8), 8.65 (1H, dd, *J*=8.0, 1.5 Hz, H10), 7.92 (1H, dd, *J*=8.0, 4.4 Hz, H9), 5.20 (2H, t, *J*=6.0 Hz, NCH_2), 3.18 (2H, t, *J*=6.0 Hz, SCH_2), 2.12 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$), 1.81 (2H, quin, *J*=6.0 Hz, $NCH_2CH_2CH_2CH_2S$); δ_C 159.6, 152.9, 145.8, 144.8, 140.1, 132.0, 130.3, 121.4, 43.6, 36.3, 29.2, 23.6; Anal. calcd for $C_{12}H_{11}N_5OS$ (273.32) C 52.73, H 4.06, N 25.62, S 11.73; Found C 52.77, H 4.10, N 25.54, S 11.79%.

4.1.26. 1,2,3,4,5,6-Hexahydro-1-oxa-6-thia-7,8,13,13a-tetraazabenzo[*f*]-[10]annuleno[1,2,3,4-*bcd*]indene (15a). δ_H 8.46 (1H, d, *J*=7.8 Hz, H10), 8.23 (1H, d, *J*=7.8 Hz, H7), 8.06 (1H, t, *J*=7.8 Hz, H9), 7.92 (1H, t, *J*=7.8 Hz, H8), 4.69, (2H, t, *J*=6.0 Hz, OCH_2), 3.10 (2H, t *J*=6.9 Hz, SCH_2), 2.18 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$), 1.65 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$); δ_C 158.6, 144.7, 144.4, 135.2, 132.1, 128.9, 125.9, 123.5, 119.3, 67.3, 33.1, 29.8, 24.6.

4.1.27. 1,2,3,4,5,6-Hexahydro-1-oxa-6-thia-7,8,9,13,13a-pentaazabenzo[*f*]-[10]annuleno[1,2,3,4-*bcd*]indene (15b). δ_H 9.12 (1H, dd, *J*=4.4,1.5 Hz, H9), 8.74 (1H, dd, *J*=7.9, 1.5 Hz, H7), 7.88 (1H, dd, *J*=7.9, 4.4 Hz, H8), 4.69 (2H, t, *J*=6.0 Hz, OCH_2), 3.11 (2H, t *J*=6.9 Hz, SCH_2), 2.18 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$), 1.64 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$); δ_C 160.0, 156.1, 146.2, 143.1, 140.4, 137.9, 121.6, 121.2, 67.1, 33.1, 30.0, 24.6.

4.1.28. 1,2,3,4,5,6-Hexahydro-1-oxa-6-thia-7,8,10,13,13a-pentaazabenzo[*f*]-[10]annuleno[1,2,3,4-*bcd*]indene (15c). δ_H 9.57 (1H,s, H10), 8.99 (1H, d, *J*=5.0 Hz, H8), 8.09 (1H, d, *J*=4.9 Hz, H7), 4.69 (2H, t, *J*=6.0 Hz, OCH_2), 3.10 (2H, t *J*=6.9 Hz, SCH_2), 2.18 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$), 1.65 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$); δ_C 160.7, 152.0, 145.7, 144.7, 144.2, 126,9 120.4, 112.5, 67.4, 33.0, 29.8, 24.7.

4.1.29. 1,2,3,4,5,6-Hexahydro-1-oxa-6-thia-7,8,11,13,13a-pentaazabenzo[*f*]-[10]annuleno[1,2,3,4-*bcd*]indene (15d). δ_H 9.45 (1H,s, H7), 9.00 (1H, d, *J*=4.9 Hz, H9), 8.22 (1H, d, *J*=4.9 Hz, H10), 4.69 (2H, t, *J*=6.0 Hz, OCH_2), 3.10 (2H, t *J*=6.9 Hz, SCH_2), 2.18 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$), 1.65 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$); δ_C 160.3, 154.0, 150.6, 144.9, 144.4, 131.3, 116.5, 114.8, 67.4, 33.1, 29.8, 24.6.

4.1.30. 1,2,3,4,5,6-Hexahydro-1-oxa-6-thia-7,8,12,13,13a-pentaazabenzo[*f*]-[10]annuleno[1,2,3,4-*bcd*]indene (15e). δ_H 9.17 (1H, dd, *J*=4.6, 1.5 Hz, H8), 8.75 (1H, dd, *J*=7.9, 1.5 Hz, H10), 7.99 (1H, dd, *J*=8.0, 4.6 Hz, H9), 4.70 (2H, t, *J*=6.0 Hz, OCH_2), 3.12 (2H, t *J*=6.9 Hz, SCH_2), 2.18 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$), 1.67 (2H, br, ~quin, $OCH_2CH_2CH_2CH_2S$); δ_C 159.9, 153.1, 144.8, 144.2, 135.8, 132.2, 130.7, 120.4, 67.3, 33.2, 29.9, 24.6.

4.2. General procedures for alkylation with iodomethane

Method A. The substrate (**1a–e**, **17a–e**: 2 mmol) and K_2CO_3 (0.149 g: 1.5 mmol) were dissolved in dry DMF (25 mL) by stirring and gentle heating under argon. Iodomethane (0.284 g: 2 mmol) was added to the clear yellow solution of **1a–e**, **17a–d** but an increased amount (1.420 g, 10 mmol) of iodomethane was added to the solution of **17e**. The resulting mixture was then stirred and kept at 100°C for 2 h. From the cooled reaction mixture of **17b** zwitterion **19b** slowly separated as pale orange crystals which was then collected and washed with cold methanol (~3–4 mL). After evaporation of the solvent in vacuo the brown residue (solid or oily) was trituated with water (5–10 mL) to obtain white solid crystals (**17a–e**) or yellow oil (**18a–e)** which were then purified by recrystallization from ethanol (**17a–e**), or solidified by treatment with methanol–water (**18a–e**).

Method B. The substrate (**1a–e**, **17a–e**: 2 mmol) was suspended in $CHCl_3$ (20 mL) under argon. To this suspension 1 M methanolic solution of Bu_4NOH (2 mL) was added and stirred for 20 min. After this period iodomethane (0.284 g: 2 mmol for **1a–e**, **17a–d** and 1.420 g: 10 mmol for **17e**) was added and the resulting mixture was refluxed for 2 h. The work-up of the reaction mixture and the purification of the products were carried out as described in Method A.

4.2.1. 3-Methylthio-[1,2,4]triazolo[3,4-*a*]phthalazine-6(5*H*)-one (17a). White needless; yield (%, by Method A/B) 72/85; mp 226–230°C; ν_{max} 3200–2780 br, 1652, 1610, 1597 cm^{-1}; δ_H 13.35 (1H, br s, N*H*), 8.50 (1H, d, *J*=7.8 Hz, H10), 8.27 (1H, d, *J*=7.8 Hz, H7), 8.10 (1H, t, *J*=7.8 Hz, H9), 7.96 (1H, t, *J*=7.8 Hz, H8), 2.84 (3H, s, SCH_3); δ_C 159.8, 147.0, 144.9, 134.9, 131.7, 126.7, 125.0, 123.0, 119.6, 14.6; Anal. calcd for $C_{10}H_8N_4OS$ (232.27) C 51.71, H 3.47, N 24.12, S 13.80; Found C 51.65, H 3.39, N 24.02, S 13.82%.

4.2.2. 3-Methylthiopyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]-pyridazine-6(5*H*)-one (17b). Yellowish cubes; yield (%,

by Method A/B) 57/73; mp 238–241°C; ν_{max} 3140–2850 br, 1649, 1605, 1592 cm^{-1}; δ_H 13.21 (1H, br s, N*H*), 9.22 (1H, dd, *J*=4.1, 1.6 Hz, H9), 8.56 (1H, dd, *J*=7.9, 1.6 Hz, H7), 8.01 (1H, dd, *J*=7.9, 4.1 Hz, H8), 2.85 (3H, s, SC*H*$_3$); δ_C 157.7, 155.8, 144.5, 142.7, 138.8, 137.5, 127.52, 125.8, 14.6; Anal. calcd for $C_9H_7N_5OS$ (233.26) C 46.34, H 3.03, N 30.03, S 13.75; Found C 46.37, H 2.98, N 29.95, S 13.79%.

4.2.3. 3-Methylthiopyrido[3,4-*d*][1,2,4]triazolo[4,3-*b*]-pyridazine-6(5*H*)-one (17c). Pale yellow powder; yield (%, by Method A/B) 82/75; mp 245–248°C; ν_{max} 3210–2700, 1662, 1611, 1599 cm^{-1}; δ_H 9.75 (1H, s, H10), 8.12 (1H, d, *J*=5.0 Hz, H8), 8.06 (1H, d, *J*=5.0 Hz, H7), 2.84 (3H, s, SC*H*$_3$); δ_C 157.7, 152.0, 145.8, 144.8, 142.2, 133.3, 121.7, 120.1, 14.6; Anal. calcd for $C_9H_7N_5OS$ (233.26) C 46.34, H 3.03, N 30.03, S 13.75; Found C 46.31, H 3.10, N 29.98, S 13.75%.

4.2.4. 3-Methylthiopyrido[4,3-*d*][1,2,4]triazolo[4,3-*b*]-pyridazine-6(5*H*)-one (17d). Yellow powder; yield (%, by Method A/B) 69/73; mp 240–244°C; ν_{max} 3200–2760, 1657, 1603, 1600 cm^{-1}; δ_H 12.88 (1H, br s N*H*), 9.35 (1H, s, H7), 9.11 (1H, d, *J*=5.0 Hz, H9), 8.34 (1H, d, *J*=5.0 Hz, H10), 2.86 (3H, s, SC*H*$_3$); δ_C 159.8, 153.6, 149.2, 146.1, 142.5, 131.4, 119.9, 112.5, 14.5; Anal. calcd for $C_9H_7N_5OS$ (233.26) C 46.34, H 3.03, N 30.03, S 13.75; Found C 46.41, H 3.07, N 29.95, S 13.69%.

4.2.5. 3-Methylthiopyrido[3,2-*d*][1,2,4]triazolo[4,3-*b*]-pyridazine-6(5*H*)-one (17e). Yellow powder; yield (%, by Method A/B) 59/75; mp 228–233°C; ν_{max} 3170–2790, 1670, 1602, 1596 cm^{-1}; δ_H 13.95 (1H, br s, N*H*), 9.20 (1H, dd, *J*=4.5, 1.5 Hz, H8), 8.93 (1H, dd, *J*=8.0, 1.5 Hz, H10), 8.08 (1H, dd, *J*=8.0, 4.5 Hz, H9), 2.85 (3H, s, SC*H*$_3$); δ_C 157.9, 153.4, 146.5, 142.4, 137.1, 132.4, 130.6, 121.3, 14.6; Anal. calcd for $C_9H_7N_5OS$ (233.26) C 46.34, H 3.03, N 30.03, S 13.75; Found C 46.38, H 3.00, N 30.11, S 13.70%.

4.2.6. 6-Methoxy-3-methylthio-[1,2,4]triazolo[3,4-*a*]-phthalazine (18a). White powder; yield (%, by Method A/B) 53/59; mp 111–112°C; ν_{max} 1622, 1594, 1533 cm^{-1}; δ_H 8.47 (1H, d, *J*=7.7 Hz, H10), 8.22 (1H, d, *J*=7.7 Hz, H7), 7.82 (1H, t, *J*=7.7 Hz, H9), 7.68 (1H, t, *J*=7.7 Hz, H8), 3.87 (3H, s, OC*H*$_3$), 2.93 (3H, s, SC*H*$_3$); δ_C 160.3, 148.2, 144.6, 134.1, 130.8, 126.2, 124.2, 123.5, 120.3, 55.7, 14.9; Anal. calcd for $C_{11}H_{10}N_4OS$ (246.30) C 53.64, H 4.09, N 22.75, S 13.02; Found C 53.70, H 4.13, N 22.68, S 12.97%.

4.2.7. 6-Methoxy-3-methylthiopyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine (18b). White powder; yield (%, by Method A/B) 47/64; mp 124–126°C; ν_{max} 1619, 1602, 1533 cm^{-1}; δ_H 9.34 (1H, dd, *J*=4.3, 1.6 Hz, H9), 8.60 (1H, dd, *J*=7.9, 1.6 Hz, H7), 8.05 (1H, dd, *J*=7.9, 4.3 Hz, H8), 3.87 (3H, s, OC*H*$_3$), 2.93 (3H, s, SC*H*$_3$); δ_C 161.8, 155.1, 144.8, 143.5, 139.4, 137.1, 128.2, 125.0, 55.7, 14.8; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.54, H 3.77, N 28.45, S 12.97%.

4.2.8. 6-Methoxy-3-methylthiopyrido[3,4-*d*][1,2,4]triazolo[4,3-*b*]pyridazine (18c). Yellowish powder; yield (%, by Method A/B) 50/54; mp 120–121°C; ν_{max} 1620, 1600, 1536 cm^{-1}; δ_H 9.80 (1H, s, H10), 9.14 (1H, d, *J*=5.0 Hz, H8), 8.15 (1H, d, *J*=5.0 Hz, H7), 3.90 (3H, s, OC*H*$_3$), 2.92 (3H, s, SC*H*$_3$); δ_C 161.7, 152.9, 145.2, 145.0, 142.7, 133.0, 121.7, 118.1, 55.9, 14.7; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.48, H 3.74, N 28.26, S 13.03%.

4.2.9. 6-Methoxy-3-methylthiopyrido[4,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine (18d). Yellow powder; yield (%, by Method A/B) 58/70; mp 114–115°C; ν_{max} 1614, 1603, 1530 cm^{-1}; δ_H 9.18 (1H, s, H7), 9.12 (1H, d, *J*=5.0 Hz, H9), 8.39 (1H, d, *J*=5.0 Hz, H10), 3.90, (3H, s, OC*H*$_3$), 2.89 (3H, s, SC*H*$_3$); δ_C 160.5, 153.0, 148.1, 147.6, 141.7, 133.0, 117.9, 113.1, 56.1, 14.6; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.56, H 3.75, N 28.36, S 13.00%.

4.2.10. 6-Methoxy-3-methylthiopyrido[3,2-*d*][1,2,4]triazolo[4,3-*b*]pyridazine (18e). Grey powder; yield (%, by Method A/B) 25/33; mp 125–126°C; ν_{max} 1628, 1601, 1534 cm^{-1}; δ_H 9.10 (1H, dd, *J*=4.8, 1.6 Hz, H8), 8.88 (1H, dd, *J*=8.0, 1.6 Hz, H10), 7.87 (1H, dd, *J*=8.0, 4.8 Hz, H9), 3.90, (3H, s, OC*H*$_3$), 2.89 (3H, s, SC*H*$_3$); δ_C 162.3, 155.1, 145.6, 142.7, 137.2, 132.0, 128.6, 117.3, 56.2, 14.6; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.49, H 3.65, N 28.25, S 13.10%.

4.2.11. 1-Methyl-3-methylthiopyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine-1-ium-6-olate (19b). Grey powder; yield (%, by Method A/B) 16/–; mp 285–290°C; ν_{max} 1611, 1592, 1546, 1525 cm^{-1}; δ_H 9.20 (1H, br d, *J*=3.9 Hz, H9), 8.71 (1H, br d, *J*=7.7 Hz, H7), 8.04 (1H, dd, *J*=7.7, 3.9 Hz, H8), 4.56 (3H, s, NC*H*$_3$), 2.81 (3H, s, SC*H*$_3$); δ_C 164.5, 153.8, 147.0, 138.0, 137.5, 136.9, 128.7, 125.4, 40.6, 13.7; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.47, H 3.72, N 28.44, S 12.99%.

4.3. Silica-catalyzed isomerization of methoxy derivatives 18a–e

The methoxy compound (1 mmol) was dissolved in $CHCl_3$ (15 mL) then silica (0.3 g, Merck grade 9385, 230–400 mesh, 60 Å) was added to the solution. The mixture was stirred for 1 h under argon. After evaporation of the reaction mixture the product (**20a–e**) was eluted with EtOAc (~50–60 mL) from the silica. The evaporation of solvent gave the product as oily residue which solidified on standing and was washed with *n*-hexane (~5 mL). Yield: 94–98%.

4.3.1. 5-Methyl-3-methylthio-[1,2,4]triazolo[3,4-*a*]-phthalazine-6(5*H*)-one (20a). White powder; mp 142–142°C; ν_{max} 1652, 1577, 1530 cm^{-1}; δ_H 8.35 (1H, d, *J*=7.9 Hz, H10), 8.28 (1H, d, *J*=7.9 Hz, H7), 7.99 (1H, t, *J*=7.9 Hz, H9), 7.66 (1H, t, *J*=7.9 Hz, H8), 4.14 (3H, s, NC*H*$_3$), 2.85 (3H, s, SC*H*$_3$); δ_C 159.5, 144.9, 144.6, 134.7, 131.3, 129.2, 124.5, 123.7, 123.5, 35.2, 17.2; Anal. calcd for $C_{11}H_{10}N_4OS$ (246.30) C 53.64, H 4.09, N 22.75, S 13.02; Found C 53.52, H 4.16, N 22.88, S 12.99%.

4.3.2. 5-Methyl-3-methylthiopyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one (20b). White powder; mp 135–136°C; ν_{max} 1658, 1570, 1535 cm^{-1}; δ_H 9.16 (1H, dd, *J*=4.3, 1.6 Hz, H9), 8.67 (1H, dd, *J*=7.9, 1.6 Hz, H7), 7.69 (1H, dd, *J*=7.9, 4.3 Hz, H8), 4.14 (3H, s, NC*H*$_3$),

2.85 (3H, s, SCH_3); δ_C 159.5, 155.1, 143.2, 143.0, 139.4, 138.2, 124.9, 121.5, 35.2, 17.3; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.66, H 3.79, N 28.41, S 12.88%.

4.3.3. 5-Methyl-3-methylthiopyrido[3,4-*d*][1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one (20c). White powder; mp 139–140°C; ν_{max} 1661, 1573, 1545 cm^{-1}; δ_H 9.60 (1H, s, H10), 8.84 (1H, d, *J*=5.1 Hz, H8), 8.11 (1H, d, *J*=5.1 Hz, H7), 4.15 (3H, s, NCH_3), 2.85 (3H, s, SCH_3); δ_C 159.5, 151.5, 145.5, 143.6, 141.8, 131.0, 121.7, 118.9, 35.3, 17.4; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.63, H 3.58, N 28.45, S 12.92%.

4.3.4. 5-Methyl-3-methylthiopyrido[4,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one (20d). Yellowish cubes; mp 122–124°C; ν_{max} 1664, 1580, 1537 cm^{-1}; δ_H 9.39 (1H, s, H7), 8.89 (1H, d, *J*=5.0 Hz, H9), 8.23 (1H, d, *J*=5.0 Hz, H10), 4.14 (3H, s, NCH_3), 2.84 (3H, s, SCH_3); δ_C 158.2, 153.4, 151.2, 144.0, 142.2, 131.5, 119.4, 115.7, 35.3, 17.4; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.49, H 3.68, N 28.49, S 13.06%.

4.3.5. 5-Methyl-3-methylthiopyrido[3,2-*d*][1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one (20e). White needless; mp 141–142°C; ν_{max} 1681, 1576, 1547 cm^{-1}; δ_H 8.91 (1H, dd, *J*=4.5, 1.6 Hz, H8), 8.82 (1H, dd, *J*=8.2, 1.6 Hz, H10), 8.01 (1H, dd, *J*=8.2, 4.5 Hz, H9), 4.14 (3H, s, NCH_3), 2.84 (3H, s, SCH_3); δ_C 157.4, 153.0, 146.2, 142.3, 139.4, 131.5, 129.9, 121.0, 35.4, 17.6; Anal. calcd for $C_{10}H_9N_5OS$ (247.28) C 48.57, H 3.67, N 28.32, S 12.97; Found C 48.44, H 3.76, N 28.39, S 13.02%.

Acknowledgements

The authors are indebted to Dr H. Medzihradszky-Schweiger for analyses.

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