SHORT PAPER

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A simple synthesis of novel 6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulenes†

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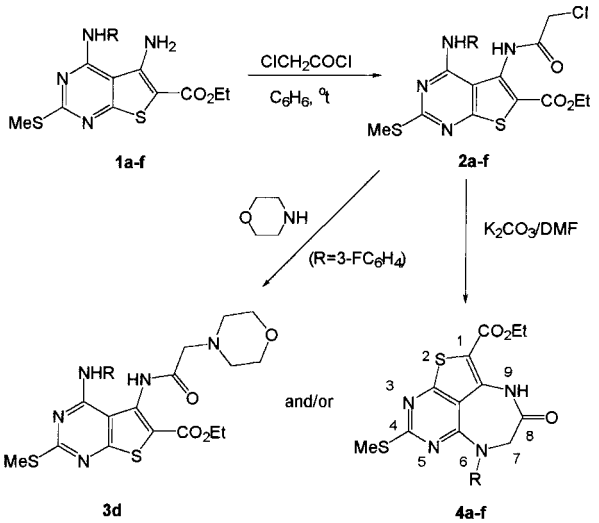
A convenient method for the synthesis of ethyl 6-substituted 6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates – representing a new heterosystem – from the corresponding ethyl 4,5-diaminothieno[2,3-*d*]pyrimidine-6-carboxylates, by a two-step protocol is described.

Despite fairly intensive research into the synthesis and the evaluation of biological properties of compounds containing the thienopyrimidine moiety,[1] very few peri-anellated systems with the thienopyrimidine skeleton are known[2] and to our knowledge no work has been done on the chemistry of 2-thia-3,5,6,9-tetraazabenz[*cd*]azulenes. In earlier papers[3] we described the preparation of 1-thia-3,5,6,8-tetraaza- and 1-thia-3,5,6,7,8-pentaazaacenaphthylenes by the cyclocondensation of 4,5-diaminothieno[2,3-*d*]pyrimidines with some one-carbon electrophilic reagents or nitrous acid. As an extension of this approach for the preparation of *peri*-anellated heterosystems containing thieno[2,3-*d*]pyrimidine moiety we now report on the synthesis of 2-thia-3,5,6,9-tetraazabenz[*cd*] azulenes, which represent a new heterocyclic system. The work was also stimulated by the reports that many compounds containing the diazepine ring possess interesting biological properties.[4]

The starting materials, ethyl 5-amino-4-(substituted amino)-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylates (**1a–f**), were synthesised using the approach first introduced by Santilli and co-workers[5] from 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile via reaction with the corresponding amines followed by the base-promoted cyclisation with ethyl mercaptoacetate.

The acetylation reaction of **1a–f** with chloroacetic acid chloride in benzene proceeded with the formation of the corresponding 5-chloroacetylamino derivatives **2a–f** as the only reaction products, *i.e.* acetylation occurred at the 5-amino group of the thienopyrimidine moiety. The direction and the yields of acetylation reaction were not affected by the electronic and steric differences of substituents in the 4-position of the thienopyrimidines.

In order to synthesise 5-(dialkylaminomethylcarboxamido)thienopyrimidines for the evaluation of their biological activity the reactions of **2d** with morpholine and piperidine were carried out. The reaction of **2d** with morpholine in ethanol led to the formation of a mixture of **3d** and **4d,** which were isolated in 27% and 16% yields, respectively. Moreover, compound **4d** was obtained as the only reaction product in the analogous reaction of **2d** with piperidine. These facts prompted us to elaborate a simple method for the preparation of 2-thia-3,5,6,9-tetraazabenz[*cd*]azulenes. The best results for the intramolecular cyclocondensations of **2a–f** to give 2-thia-3,5,6,9-tetraazabenz[*cd*]azulenes **4a–f** were obtained when the reactions were carried out in DMF at 70–80°C in the presence of K_2CO_3. The structures of all the synthesised compounds were confirmed by their elemental and spectral data. For example, in the ^{1}H NMR spectrum of **2a, a** doublet at 2.95 ppm for the protons of the NCH_3 group and a singlet at 10.17 ppm for the NHCO group were observed, while in the spectrum of **4a** the signal for the protons of the NCH_3 group appeared as a singlet at 3.31 ppm. The characteristic quartet for N*H*CH_3, which was observed at 7.25 ppm in the spectrum of **2a**, disappeared from the spectrum of the tricyclic **4a.**



Scheme 1

Experimental

M.p.s were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT spectrophotometer Spectrum BX II. NMR spectra were recorded on Bruker AC 300, 250 or Tesla 570A spectrometers using tetramethylsilane as internal standard. Mass spectra were obtained on a MAT 8500 instrument using an ionising energy of 70 eV and introduction by direct insertion probe. Microanalyses were performed by the Microanalysis Laboratory of the Department of Organic Chemistry of Vilnius University.

The synthesis of compounds **1a,b** is described in ref. 3a, compounds **1c–f** in ref. 6.

Ethyl 5-(chloroacetylamino)-4-(substituted-amino)-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylates **(2a–f):** *General procedure*: To a mixture of the corresponding **1a–f** (2.65 mmol) in benzene (30 ml), chloroacetic acid chloride (0.39 g, 3.45 mmol) was added dropwise. The reaction mixture was refluxed for 6 h and then cooled to room temperature. The precipitate was filtered off, and recrystallised to give compounds **2a–f**. The results are listed in Table 1.

Interaction of ethyl 5-(chloroacetylamino)-4-(3-fluoropheny-

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Physical and analytical data for compounds **2a–f**

Compound (yield, %)	M.p. (*T*/°C) (solvent)	Found (required) (%) C	H	N	ν_{max}/cm^{-1}	δ_H[a]
2a (66)	173–174 (MeOH)	41.6 (41.65)	3.7 (4.0)	14.9 (14.95)	3385, 3320 (NH) 1682, 1674 (CO)	1.25 (3 H, t, CH_3), 2.49 (3 H, s, SCH_3), 2.95 (3 H, d, NCH_3), 4.24 (2 H, q, OCH2), 4.43 (2 H, s, CH_2Cl), 7.25 (1 H, q, NH), 10.17 (1 H, s, NHCO)
2b (68)	178–179 (EtOH)	46.4 (46.1)	5.2 (5.1)	13.5 (13.4)	3384, 3344 (NH) 1680, 1664 (CO)	0.96 (3 H, t, CH_3), 1.2–1.65 (7 H, m, CH_2CH_2, CH_3), 2.58 (3 H, s, SCH_3), 3.57 (2 H, q, NCH_2), 4.22 (2 H, s, CH_2Cl), 4.37 (2 H, q, OCH_2), 6.0 (1 H, t, NH), 9.72 (1 H, s, NHCO)
2c (80)	212–214 (C_6H_6)	47.2 (47.5)	3.7 (3.5)	12.4 (12.3)	3416, 3232 (NH) 1700, 1678 (CO)	1.38 (3 H, t, CH_3), 2.60 (3 H, s, SCH_3), 4.34 (2 H, s, CH_2Cl), 4.4 (2 H, q, OCH_2), 7.0-7.3 (3 H, m, aromatic prot.), 8.1 (1 H, s, NH), 8.45-8.7 (1 H, m, aromatic prot.), 9.71 (1 H, s, NHCO)
2d (91)	208–209 (Dioxane)	47.4 (47.5)	3.7 (3.5)	12.2 (12.3)	3384, 3328 (NH) 1688, 1664 (CO)	1.09 (3 H, t, CH_3), 2.23 (3 H, s, SCH_3), 4.10 (2 H, s, CH_2Cl), 4.20 (2H, q, OCH_2), 6.68–7.2 (4 H, m, aromatic prot.)
2e (83)	217–218 (Dioxane)	47.4 (47.5)	3.7 (3.55)	12.2 (12.3)	3320, 3224 (NH) 1688, 1674 (CO)	1.08 (3 H, t, CH_3), 2.15 (3 H, s, SCH_3), 3.90–4.35 (4 H, m, OCH_2, CH_2Cl), 6.60–7.2 (4 H, m, aromatic prot.)
2f (74)	183.5–185 (Dioxane)	45.0 (45.2)	3.5 (3.2)	10.9 (11.1)	3400, 3312 (NH) 1684, 1648 (CO)	1.08 (3 H, t, CH_3), 2.21 (3 H, s, SCH_3), 4.11 (2 H, s, CH_2Cl), 4.20 (2 H, q, OCH_2), 7.11–7.4 (3 H, m, aromatic prot.), 7.52–7.65 (1 H, m, aromatic prot.)

[a]^{1}H NMR spectra of compound **2a** was recorded in DMSO-D_6, **2b,c** in $CDCl_3$, **2d-f** in CF_3COOD.

Table 2 Physical and analytical data for compounds **4a–f**

Compound (yield, %)	M.p. (*T*/°C) (solvent)	Found (required) (%) C	H	N	ν_{max}/cm^{-1}	δ_H[a]	δ_C
4a[b] (63)	217.5–218.5 (Pr^iOH)	46.3 (46.1)	4.3 (4.2)	16.3 (16.6)	3295 (NH) 1694, 1674 (CO)	1.39 (3 H, t, CH_3), 2.53 (3 H, s, SCH_3), 3.31 (3 H, s, NCH_3), 4.11 (2 H, s, $COCH_2$), 4.36 (2 H, q, OCH_2), 10.08 (1 H, s, NHCO)	–
4b (71)	153–154 (EtOH)	50.6 (50.5)	5.5 (5.3)	14.8 (14.7)	3300 (NH) 1684, 1664 (CO)	0.96 (3 H, t, CH_3), 1.3–1.48 (5 H, m, CH_2, CH_3), 1.62–1.78 (2 H, m, CH_2), 2.56 (3 H, s, SCH_3), 3.8 (2 H, t, NCH_2), 4.12 (2 H, s, $COCH_2$), 4.36 (2 H, q, OCH_2), 10.13 (1 H, s, NHCO)	13.7, 14.2, 14.3, 19.9, 29.2, 49.9, 55.8, 61.5, 100.6, 108.1, 137.1, 158.9, 163.9, 165.5, 168.1, 170.7
4c (96)	191–194 (CCl_4)	51.5 (51.7)	3.7 (3.6)	13.5 (13.4)	3280 (NH) 1672, 1660 (CO)	1.35 (3 H, t, CH_3), 2.28 (3 H, s, SCH_3), 4.35 (2 H, q, OCH_2), 4.7 (2 H, s, $COCH_2$), 7.3–7.62 (4 H, m, aromatic prot.), 10.2 (1 H, s, NHCO)	13.65, 14.3, 57.5, 61.7, 101.5, 109.1, 125.5, 128.45, 130.4, 130.6, 136.9, 155.2, 158.6, 159.1, 162.9, 165.45, 167.7, 170.1
4d[b] (89)	195–196 (DMF-H_2O)	51.3 (51.7)	3.75 (3.6)	13.6 (13.4)	3250 (NH) 1664, 1648 (CO)	1.39 (3 H, t, CH_3), 2.31 (3 H, s, SCH_3), 4.41 (2 H, q, OCH_2), 4.45 (2 H, s, $COCH_2$), 7.04–7.15 (4 H, m, aromatic prot.), 10.27 (1 H, s, NH)	–
4e (93)	186–189 (C_6H_6)	51.8 (51.7)	3.8 (3.6)	13.7 (13.4)	3285 (NH) 1672, 1664 (CO)	1.38 (3 H, t, CH_3), 2.28 (3 H, s, SCH_3), 4.35 (2 H, q, OCH_2), 4.69 (2 H, s, $COCH_2$), 7.25–7.4 (2 H, m, aromatic prot.), 7.4–7.6 (2 H, m, aromatic prot.), 10.18 (1 H, s, NHCO)	13.4, 14.0, 57.5, 61.4, 100.4, 108.9, 115.6, 116.0, 128.3, 128.4, 136.95, 139.2, 139.25, 158.8, 162.7, 165.2, 167.45, 169.6
4f (90)	222–224 (C_6H_6)	48.8 (48.7)	3.5 (3.2)	12.1 (12.0)	3284 (NH) 1688, 1664 (CO)	1.48 (3 H, t, CH_3), 2.38 (3 H, s, SCH_3), 4.52 (2 H, q, OCH_2), 4.99 (2 H, s, $COCH_2$), 7.58–7.94 (4 H, m, aromatic prot.)	13.33, 13.73, 58.12, 64.50, 107.45, 109.36, 117.33, 121.22, 123.81, 129.24, 131.42, 133.06, 135.25, 141.61, 157.04, 158.62, 163.26, 165.90, 167.46

[a]NMR spectra of compounds **4a,c,e** were obtained in DMSO-D_6, **4b,d** in $CDCl_3$, **4f** in CF_3COOD
[b]^{13}C NMR spectra were not recorded because of the insufficient solubility of compounds **4a,d**.

MS *m/z* (%) **4b** 380 (M^+, 100), **4c** 418 (M^+, 100), **4d** 418 (M^+, 100), **4e** (418 (M^+, 100), **4f** 468 (M^+, 100).

lamino)-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate **(2d)** *with morpholine:* A mixture of **2d** (0.5 g, 1.1 mmol), morpholine (0.19 g, 2.2 mmol) and EtOH (15 ml) was refluxed for 3.5 h. After cooling to room temperature the precipitate was filtered off, the filtrate was concentrated under reduced pressure to one third its volume and cooled. The precipitate was filtered off, combined with the obtained earlier and chromatographed on a column with silica gel (40–100 μm), eluent chloroform – ethyl acetate (5:1 v/v). From the fraction with R_f 0.47 after evaporation of solvent and recrystallisation 0.09 g (16%) of compound **4d** was obtained. The results are listed in Table 2. Analogous work-up of the fraction with R_f 0.32 furnished 0.15 g (27%) of compound **3d**. M.p. 167–168 °C (from ethanol). IR

(Nujol) ν_{max}/cm^{-1} 3280 (NH), 1696, 1672 (CO); ^1H NMR ($CDCl_3$, 80 MHz) δ 1.39 (3H, t, CH_3), 2.58 (3H, s, SCH_3), 2.62–2.83 (4H, m, NCH_2), 3.32 (2H, s, $COCH_2$), 3.75–3.98 (4H, m, CH_2O), 4.36 (2H, q, OCH_2), 7.19–7.63 (4H, m, aromatic prot.), 9.17 (1H, br s, NH) and 10.99 (1H, br s, NH); MS *m/z* (%) 505 (M^+, 7) (Found: C, 52.0; H, 4.7; N, 13.6. $C_{22}H_{24}FN_5O_4S_2$ requires C, 52.3; H, 4.8; N, 13.85%).

Ethyl 4-methylthio-8-oxo-6-substituted 6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[cd]azulene-1-carboxylates **(4a–f)**. *General procedure*: A mixture of the corresponding **2a–f** (1.1 mmol), K_2CO_3 (0.65 g, 0.65 mmol) and dry DMF (15 ml) was heated at 70–80°C for 3–6 h. Then the reaction mixture was poured to water, the precipitate was filtered off and recrystallised to give compounds **4a–f**. The results are listed in Tables 1 and 2.

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