Chemistry of Heterocyclic Compounds, Vol. 32, No. 1, 1996

SYNTHESIS OF 3,4-DIHYDRO-5H-1-THIA-3,5,6,8-TETRAAZAACENAPHTHYLENES

S. Tumkyavichyus

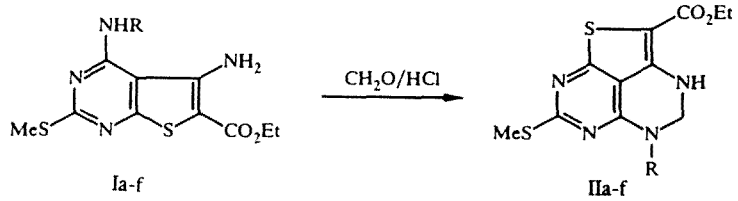
Reaction of ethyl 5-amino-4-(substituted amino)-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylates with formaldehyde in the presence of hydrochloric acid resulted in the synthesis of the corresponding ethyl 3,4-dihydro-7-methylthio-5H-1-thia-3,5,6,8-tetraazaacenaphthylene-2-carboxylates, which are examples of a new heterocyclic system.

Esters and amides of 5-aminothieno[2,3-d]pyrimidine-6-carboxylic acids can enter into the cyclocondensation reaction with different reagents to form linear tricyclic heterocycles containing the thieno[2,3-d]pyrimidine fragment [1, 2]. The work [2] also utilized esters and amides of some 4,5-diaminothieno[2,3-d]pyrimidine-6-carboxylic acids for this purpose. However, it was shown that the products of the cyclocondenstion reactions with urea, formamide, orthoformic ester, methyl isothiocyanate, phenyl isocyanate, and nitrous acid have the structure of linear heterosystems, although the reaction of some reagents could also occur with the amino groups at the positions 4 and 5 of thienopyrimidne. In this connection, and in the continuation of investigations in the series of thieno[2,3-d]pyrimidine heterocycles [3-6], it was of interest to study the possible formation of derivatives of the pericyclic heterocycle 3,4-dihydro-5H-1-thia-3,5,6,8-tetraazaacenaphthylene using the example of the reduction of ethyl 4,5-diamino-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylates with formaldehyde.

Moreover, the present investigation was stimulated by communications concerning the valuable pharmacological properties of polyazaacenaphthylenes [7-10] as well as the case that the literature only has a few examples of the synthesis of pericondensed heterosystems containing thienopyrimidine structural units [11-13].

The initial compounds — ethyl 5-amino-4-(substituted amino)-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylates (I) — were synthesized by the reaction of 4-(substituted amino)-2-methylthio-6-chloropyrimidine-5-carbonitriles with ethyl mercaptoacetate in the presence of sodium ethoxide [14, 15]. When the compound (I) is boiled with 32% Formalin in ethanol in the presence of a catalytic amount of hydrochloric acid, the cyclocondensation reaction between the amino groups of the thienopyrimidine and the formaldehyde proceeds with the formation of the corresponding 3,4-dihydro-5H-1-thia-3,5,6,8-tetraazaacenaphthylenes (II). The yields of the products are 58-96%. Differences in the steric and electronic properties of the substituents at the position 4 of the thienopyrimidines (I) exert practically no influence on the duration of the reactions and the yields of the products. It should be noted that the cyclocondensation reaction only proceeds in the presence of hydrochloric acid.

The spectral properties and the data of the elemental analysis of the 3,4-dihydro-5H-1-thia-3,5,6,8-tetraazaacenaphthylenes (IIa-f) obtained correspond with their structure. The mass spectrum of compound (IIa) contains the peak of the molecular ion with the *m/z* 310 corresponding with its molecular mass. The IR spectra of the compounds (IIa-f) reveal one



Ia-f IIa-f

I, II a R = Me, b R = *i*-Pr, c R = cyclo-Pr, d R = Bu, e R = *p*-BrC_6H_4, f R = *o*-ClC_6H_4

Vil'nyus University, Vil'nyus 2006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 103-105, January, 1996. Original article submitted June 1, 1995.

0009-3122/96/3201-0093$15.00

TABLE 1. Characteristics of the Compounds (IIa-f)

Compound	mp, °C (solvent)	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm ($CDCl_3$)	Yield, %
IIa	195...196,5 (EtOH)	3408 (NH), 1656 (CO)	1,34 (3H, t, CH_3), 2,55 (3H, s, SCH_3), 3,13 (3H, s, NCH_3), 4,29 (2H, q, OCH_2), 4,68 (2H, s, CH_2), 6,10 (1H, broad. s, NH)	96
IIb	167...169 (EtOAc)	3352 (NH), 1664 (CO)	1,27 (6H, d, $2CH_3$), 1,34 (3H, t, CH_3), 2,56 (3H, s, SCH_3), 4,29 (2H, q, OCH_2), 4,68 (2H, s, CH_2), 4,97 (1H, m, CH), 6,11 (1H, broad. t, NH)	77
IIc	207...208,5 (dioxane–Etoh)	3384 (NH), 1656 (CO)	0,87 (4H, m, $2CH_2$), 2,58 (3H, s, SCH_3), 2,77 (1H, m, NCH), 4,28 (2H, q, OCH_2), 4,74 (2H, s, CH_2), 6,2 (1H, broad. s, NH)	64
IId	127...129 (EtOH)	3384 (NH), 1656 (CO)	0,95 (3H, t, CH_3), 1,35 (3H, t, CH_3), 1,59 (4H, m, CH_2CH_2), 2,56 (3H, s, SCH_3), 3,63 (2H, t, NCH_2), 4,3 (2H, q, OCH_2), 4,73 (2H, s, CH_2), 6,07 (1H, broad. s, NH)	58
IIe	228...230 (dioxane)	3320 (NH), 1684 (CO)	1,05 (3H, t, CH_3), 2,15 (3H, s, SCH_3), 4,08 (2H, q, OCH_2), 5,03 (2H, s, CH_2), 6,93 (2H, d, aromatic proton), 7,31 (2H, d, aromatic proton)	88
IIf	196,5...198 (dioxane–Etoh)	3400 (NH), 1664 (CO)	1,36 (3H, t, CH_3), 2,38 (3H, s, SCH_3), 4,32 (2H, q, OCH_2), 5,0 (2H, s, CH_2), 6,29 (1H, s, NH), 7,37 (4H, m, aromatic proton)	71

*The ^1H NMR spectrum was taken in CF_3COOD.

TABLE 2. Data of the Elemental Analysis of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %		
		C	H	N
IIa	$C_{12}H_{14}N_4O_2S_2$	46,56 / 46,43	5,00 / 4,55	18,00 / 18,05
IIb	$C_{14}H_{18}N_4O_2S_2$	49,85 / 49,68	5,31 / 5,36	16,58 / 16,56
IIc	$C_{14}H_{16}N_4O_2S_2$	50,17 / 49,98	4,64 / 4,79	16,72 / 16,65
IId	$C_{15}H_{20}N_4O_2S_2$	51,14 / 51,11	5,62 / 5,72	15,83 / 15,89
IIe	$C_{17}H_{15}BrN_4O_2S_2$	45,53 / 45,24	3,43 / 3,35	12,56 / 12,41
IIf	$C_{17}H_{15}ClN_4O_2S_2$	50,32 / 50,18	3,58 / 3,72	13,85 / 13,77

absorption band in the region of 3408-3320 cm^{-1}, caused by the stretching vibrations of the N–H bond, and the absorption band of the carbonyl group at 1684-1656 cm^{-1}. Characteristic differences in the 1H NMR spectra of the compounds (IIa-f) by comparison with the spectra of the initial thienopyrimidines (Ia-f) are the appearance of singlets of the methylene group of the fourth position in the region of 4.68-5.03 ppm, the disappearance of the signals of the secondary amino group, the protons of which resonate in the region of 5.47-7.35 ppm in the 1H NMR spectra of compounds (Ia-f) [14, 15], and the change in the multiplicity of the signals of the N–CH groups in the fifth position. For example, the protons of the $N-CH_3$ group of compound (IIa) resonate in the form of a singlet at 3.13 ppm, whereas the signals of the protons of this group in compound (Ia) [14] appear at 3.09 ppm in the form of a doublet.

Therefore, the proposed reaction scheme enables compounds of a new type, presenting interest for chemical and biological investigations, to be synthesized.

EXPERIMENTAL

The IR spectra were recorded using mineral oil and the Specord M-80 instrument. The 1H NMR spectra were obtained on the Tesla BS-587 A spectrometer (80 MHz) using TMS as the internal standard. The mass spectrum of compound (IIa) was taken on the Hewlett Packard 5890/5971 GC/MS instrument. Monitoring of the course of reactions and the purity of the com-

pounds obtained was performed by the method of TLC on plates of DC-Alufolien aluminum oxide 150 F 254 neutral (Type T), with development in UV light.

Ethyl Esters of 5-Substituted 3,4-Dihydro-7-methylthio-5H-1-thia-3,5,6,8-tetraazaacenaphthylene-2-carboxylic Acids (IIa-f). General Method. To the mixure of the compounds (Ia-f) (1 mmole), are added 1-2 drops of concentrated hydrochloric acid, and the mixture is boiled with stirring for 2.5-3.5 h. After the cooling of the reaction mixture to room temperature, the residue is filtered off and recrystallized. The characteristics of the compounds (IIa-f) are presented in Table. 1.

REFERENCES

1. W. Ried and G. Beller, Liebigs Ann. Chem., 633 (1988).
2. J. Clark and G. Hitiris, J. Chem. Soc. Perkin Trans. I, 2005 (1984).
3. S. P. Tumkyavichyus and R. I. Matulyanuskene, Khim. Geterotsikl. Soedin., No. 8, 1131 (1987).
4. S. P. Tumkyavichyus, Khim. Geterotsikl. Soedin., No. 11, 1559 (1988).
5. S. Tumkyavichyus [Tumkavicius] and J. Mickiene, Org. Prep. Proc. Int., **23**, 413 (1991).
6. S. Tumkyavichyus [Tumkavicius], J. Prakt. Chem., **336**, 160 (1994).
7. A. Dlugosz, Arch. Pharm., **322**, 599 (1989).
8. J. J. Levin, J. W. Epstein, B. Bear, W. D. Dean, J. P. Dusza, S. S. Tseng, H. J. Schwritzer, G. D. Francisco, and W. T. Cain, Bioorg. Med. Chem. Lett., **1**, 435 (1991).
9. Jpn. Pat. 04,211,063; H. Akimoto, K. Otsu, and T. Miwa, Chem. Abs., **118**, 213100.
10. A. Sickle, A. M. Kawasaki, and L. B. Townsend, Heterocycles, **30**, 963 (1990).
11. A. N. Grinev and N. V. Kaplina, Khim. Geterotsikl. Soedin., No. 7, 925 (1985).
12. R. K. Russel, R. A. Rampulla, C. E. Nievelt, and D. H. Klaubert, J. Heterocycl. Chem., **27**, 1761 (1990).
13. US Pat. 4939137; R. K. Russel and R. A. Rampulla, Chem. Abs., **113**, 212008 (1990).
14. S. Tumkyavichyus [Tumkavicius] and R. Pupeikyte, J. Chem. Res., No. 7, 286 (1995).
15. S. Tumkyavichyus [Tumkavicius], Liebigs Ann., No. 9, 1703 (1995).