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Translated by J. Šraga

Reactions of 2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with Nitrogen Nucleophiles

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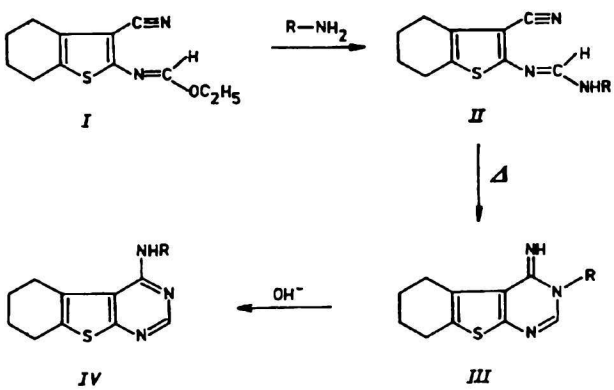
Received 23 November 1990

2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene gave in the reaction with nitrogen nucleophiles corresponding formamidines that under heating cyclized to 3-substituted 4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-3,4-dihydropyrimidines. These under a base catalysis underwent Dimroth rearrangement to 4-substituted 5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines.

2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (*I*) is mentioned in the paper [1] as a substrate in the reaction with methylamine and in the paper [2] its reaction with hydrazine hydrate leading to the product of the type of formamidines is described. This was then employed for the preparation of a fused heterocyclic derivative — triazolo[2,3-*c*]pyrimidine.

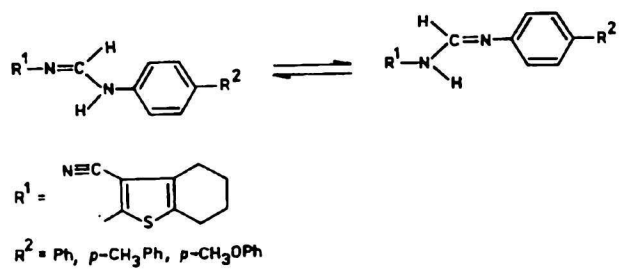


R		R	
a	CH_3CH_2	*e*	*p*-NO_2Ph
b	Ph	*f*	NH_2
c	*p*-CH_3Ph	*g*	PhNH
d	*p*-CH_3OPh	*h*	NH=C(NH_2)

Scheme 1

The aim of our work was to check the behaviour of *I* against a broader scale of nucleophile representatives and compare their reaction conditions.

There are two reactive centres sensitive to nucleophilic attack in the structure of used compound *I*. But in all our tested cases of the reaction of *I* with nitrogen nucleophiles the only attack on the double bond C=N was observed under formation of formamidines *II* (Scheme 1). The reactions were carried out with ethylamine, aniline, *p*-toluidine, *p*-anisidine, *p*-nitroaniline, hydrazine, phenylhydrazine, guanidine, and urea.



Scheme 2

In case of the reaction of compound *I* with strong nucleophiles the formed formamidines (compounds *IIf*—*IIh*) could not be isolated because

these immediately entered into cyclization to compounds *III*. Compound *IIa* appeared as an exception. We succeeded to isolate it only due to its bad solubility in benzene used as the solvent in the reaction with ethylamine. When the same reaction was carried out in ethanol, immediate cyclization to compound *III* was observed. The opposite is the reaction of aniline and its substituted derivatives where the completion of the reaction to compound *II* lasted several hours (the reaction was monitored by TLC). We did not succeed in realizing the reaction with urea probably due to low nucleophility of its nitrogen atom.

The cyclizations of compounds *II*, isolated as intermediates, were at first carried out in boiling ethanol. But because of their low reactivity in that solvent (an exception was compound *IIa*) we approved high boiling solvent decalin. However, *p*-nitrophenyl-substituted derivative *IIe* cyclized to compound *IIIe* very slowly as it might be expected due to the low nucleophility of the nitrogen atom and its formation could be monitored only by chromatography without a product isolation.

The course of the reaction was followed by TLC. The presence of the stretching vibration of the cyano group in the spectrum of isolated product served for distinguishing whether the product is formamidine *II* or already cyclic product *III*. Also ^{1}H NMR spectra very well supported the structure of the cyclic form. In the starting compound *IIa* one can observe interaction and splitting of the hydrogen atoms signals in =C—H and —NH—R groups to doublets. In ^{1}H NMR spectra of phenyl-substituted formamidines (*IIb*—*IId*) there are two signals of hydrogen atom bound to the nitrogen atom with the only half integral intensity as well as a broad diffusion band of aromatic protons. This fact could be explained by the existence of

Table 1. Characteristics of Synthesized Compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C
			C	H	N		Solvent
IIa	$C_{12}H_{15}N_3S$	233.21	61.80	6.43	18.02	73	151—153
			61.53	6.28	17.60		Ethyl acetate
IIb	$C_{16}H_{15}N_3S$	281.25	68.33	5.33	14.94	68	162—164
			68.11	5.52	14.62		Toluene
IIc	$C_{17}H_{17}N_3S$	295.26	69.16	5.75	14.23	61	154—156
			68.97	5.82	14.00		Toluene
IId	$C_{17}H_{17}N_3OS$	311.26	65.60	5.46	13.50	68	148—151
			65.45	5.33	13.15		Toluene
IIe	$C_{16}H_{14}N_4O_2S$	326.26	58.90	4.29	17.17	0.5	153—156
			58.63	3.97	17.95		Toluene
IIIa	$C_{12}H_{15}N_3S$	233.21	61.80	6.43	18.02	88	84—86
			61.62	6.13	18.23		Tetrachloromethane
IIIb	$C_{16}H_{15}N_3S$	281.25	68.33	5.33	14.94	51	173—175
			68.12	5.25	14.68		Ethyl acetate
IIIc	$C_{17}H_{17}N_3S$	295.26	69.16	5.75	14.23	41	145—147
			69.03	5.48	14.02		Ethyl acetate
IIId	$C_{17}H_{17}N_3OS$	311.26	65.60	5.46	13.50	65	145—146
			65.39	5.11	13.04		Ethyl acetate
IIIf	$C_{10}H_{12}N_4S$	220.20	54.54	5.44	25.44	92	147—149
			54.49	5.23	25.12		Toluene
IIIg	$C_{16}H_{16}N_4S$	296.26	64.87	5.40	18.91	69	169—171
			64.53	5.19	18.96		Toluene
IIIh	$C_{11}H_{13}N_5S$	247.22	53.44	5.25	28.33	89	266—267
			53.15	5.03	28.04		Ethanol
IVa	$C_{12}H_{15}N_3S$	233.21	61.80	6.43	18.02	65	153
			61.55	6.46	18.23		Ethyl acetate
IVb	$C_{16}H_{15}N_3S$	281.25	68.33	5.33	14.94	80	168—169
			67.99	5.11	14.69		Ethyl acetate
IVc	$C_{17}H_{17}N_3S$	295.26	69.16	5.75	14.23	75	145—147
			69.00	5.43	14.03		Ethyl acetate
IVd	$C_{17}H_{17}N_3OS$	311.26	65.60	5.46	13.50	95	142—143
			65.41	5.31	13.03		Ethyl acetate
IVf	$C_{10}H_{12}N_4S$	220.20	54.54	5.44	25.44	30	182—185
			54.24	5.17	25.12		Water+ethanol
IVg	$C_{16}H_{16}N_4S$	296.26	64.87	5.40	18.91	50	235—238
			64.53	5.12	18.69		Ethyl acetate
IVh	$C_{11}H_{13}N_5S$	247.22	53.44	5.25	28.33	75	268
			53.12	5.16	28.04		Ethanol

Table 2. IR Spectral Data of Synthesized Compounds

Compound	$\tilde{\nu}$/cm^{-1}				
	ν(C=C)	ν(C≡N)	ν(C—H)	ν(N—H)	
IIa	1630	2210	2950	3390	
IIb	1635	2210	2950	3340	
IIc	1635	2210	2950	3340	
IId	1630	2210	2950	3340	
IIe	1605	2220	2940	3440	
IIIa	1615		2950	3330	
IIIb	1600		2930	3310	
IIIc	1610		2940	3310	
IIId	1610		2940	3310	
IIIf	1620		2930	3250	3320
IIIg	1625		2950	3290	3340
IIIh	1605		2930	3280	3320
				3350	3400
IVa	1590		2950	3430	
IVb	1600		2940	3390	
IVc	1600		2940	3390	
IVd	1605		2940	3390	
IVf	1625		2940	3260 br	3380
IVg	1620		2950	3330	3340
IVh	1610		2950	3300 br	

a quick dynamic equilibrium between the tautomeric forms shown in Scheme 2 which are approximately equally stable in the used solvents.

As it is known from the literature [3] Dimroth rearrangement is catalyzed by a base. Therefore we tried to achieve the rearrangement of *III* to *IV* in ethanol in the presence of a catalytic amount of sodium hydroxide. The formation of the product of the rearrangement and the course of it was monitored by TLC. Products *III* and *IV* differed in their ^{1}H NMR spectra (Table 3). The spectrum of compound *III* is characterized by the resolution of the multiplet with integral intensity equal to 4 that corresponds to the hydrogen atoms of CH_2 groups of the condensed cyclohexane ring to two separated signals with integral intensity equal to 2. This separation is not observed in the spectrum of either compounds *II* or compounds *IV*.

Very interesting are also the electronic spectra of compounds *III* and *IV* (Table 4). The absorption band in the spectrum of compounds *III* corresponding to the π—π^* transition, is in the spectrum of compounds *IV* bathochromically shifted into the region where compounds *III* showed absorption band corresponding to the n—π^* transition.

Table 3. ^{1}H NMR Spectral Data of Synthesized Compounds

Compound	δ
IIa	1.24 (t, 3H, J = 7.5 Hz, CH_3), 1.74–1.87 (m, 4H, CH_2), 2.50–2.62 (m, 4H, CH_2), 2.92–3.72 (m, 2H, CH_2), 5.12–5.92 (br, 1H, NH), 7.78 (d, 1H, J = 4 Hz, =CH)
IIb[a]	1.75–1.95 (m, 4H, CH_2), 2.45–2.77 (m, 4H, CH_2), 7.13 (d, 1H, J = 8.4 Hz, =CH), 7.30–7.58 (m, 5H, H_{arom}), 8.12–8.72 (br, 0.5 H, NH), 9.16–9.96 (br, 0.5 H, NH)
IIc	1.71–1.95 (m, 4H, CH_2), 2.32 (s, 3H, CH_3), 2.53–2.73 (m, 4H, CH_2), 6.80–7.28 (m, 5.5 H, H_{arom}, NH, =CH), 8.31 (br, 0.5 H, NH)
IId[a]	1.70–1.85 (m, 4H, CH_2), 2.40–2.63 (m, 4H, CH_2), 3.73 (s, 3H, OCH_3), 6.85–7.03 (m, 5H, H_{arom}, =CH), 7.13–7.43 (br, 0.5 H, NH), 7.70–8.03 (br, 0.5 H, NH)
IIe	1.75–2.05 (m, 4H, CH_2), 2.55–2.76 (m, 4H, CH_2), 4.05–4.70 (br, 1H, NH), 6.63 (d, 2H, J = 8.9 Hz, H_{arom}), 8.07 (d, 2H, J = 8.9 Hz, H_{arom}), 8.24 (d, 1H, J = 9 Hz, =CH)
IIIa	1.38 (t, 3H, J = 7.5 Hz, CH_3), 1.81–1.93 (m, 4H, CH_2), 2.70–2.88 (m, 2H, CH_2), 2.88–3.05 (m, 2H, CH_2), 4.02 (q, 2H, J = 7.5 Hz, CH_2), 6.71 (s, 1H, NH), 7.62 (s, 1H, =CH)
IIIb	1.83–2.20 (m, 4H, CH_2), 2.78–3.00 (m, 2H, CH_2), 3.00–3.20 (m, 2H, CH_2), 7.10–7.80 (m, 5H, H_{arom}), 7.13 (s, 1H, NH), 8.49 (s, 1H,=CH)
IIIc	1.73–2.03 (m, 4H, CH_2), 2.44 (s, 3H, CH_3), 2.68–2.91 (m, 2H, CH_2), 2.91–3.13 (m, 2H, CH_2), 7.20–7.53 (m, 4H, H_{arom}), 7.26 (s, 1H, NH), 7.59 (s, 1H, =CH)
IIId	1.78–1.95 (m, 4H, CH_2), 2.70–2.91 (m, 2H, CH_2), 2.91–3.13 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.40 (s, 1H, NH), 7.04 (d, 2H, J = 8.9 Hz, H_{arom}), 7.27 (d, 2H, J = 8.9 Hz, H_{arom}), 7.59 (s, 1H, =CH)
IIIf	1.81–1.99 (m, 4H, CH_2), 2.74–2.85 (m, 2H, CH_2), 2.85–2.99 (m, 2H, CH_2), 4.76 (s, 2H, NH_2), 6.25–7.35 (br, 1H, NH), 7.94 (s, 1H, =CH)
IIIg	1.75–1.97 (m, 4H, CH_2), 2.70–3.03 (m, 4H, CH_2), 6.83–7.45 (m, 7H, H_{arom}, NH, =NH), 7.88 (s, 1H, =CH)
IIIh[b]	1.43–2.10 (m, 4H, CH_2), 2.33–3.17 (m, 4H, CH_2), 5.70–6.30 (m, 2H, NH_2), 7.90 (s, 1H, =CH), 8.22 (s, 1H, NH), 8.34 (s, 1H, NH)
IVa	1.30 (t, 3H, J = 7.5 Hz, CH_3), 1.85–1.97 (m, 4H, CH_2), 2.73–3.05 (m, 4H, CH_2), 3.60 (dq, 2H, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 5.1 Hz, CH_2), 5.15–5.43 (br, 1H, NH), 8.38 (s, 1H, =CH)
IVb	1.83–2.11 (m, 4H, CH_2), 2.81–3.12 (m, 4H, CH_2), 7.03–7.70 (m, 6H, H_{arom}, NH), 8.48 (s, 1H, =CH)
IVc	1.88–2.16 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.80–3.20 (m, 4H, CH_2), 7.06 (s, 1H, NH), 7.18 (d, 2H, J = 8.4 Hz, H_{arom}), 7.50 (d, 2H, J = 8.4 Hz, H_{arom}), 8.46 (s, 1H, =CH)
IVd	1.84–2.12 (m, 4H, CH_2), 2.76–3.20 (m, 4H, CH_2), 3.82 (s, 3H, OCH_3), 6.97 (d, 2H, J = 8.5 Hz, H_{arom}), 7.00 (s, 1H, NH), 7.64 (d, 2H, J = 8.5 Hz, H_{arom}), 8.43 (s, 1H, =CH)
IVf	1.85–2.05 (m, 4H, CH_2), 2.75–3.05 (m, 4H, CH_2), 3.60 (s, 2H, NH_2), 6.40 (s, 1H, NH), 8.45 (s, 1H, =CH)
IVg[b]	1.73–2.00 (m, 4H, CH_2), 2.68–3.10 (m, 4H, CH_2), 6.82–7.43 (m, 7H, H_{arom}, 2 NH), 7.86 (s, 1H, =CH)
IVh[b]	1.73–2.00 (m, 4H, CH_2), 2.68–3.10 (m, 4H, CH_2), 3.32 (s,1H, NH), 6.80 (s, 3H, NH_2, =NH), 8.19 (s, 1H, =CH)

a) Measured in $(CD_3)_2CO$, *b*) in DMSO-d_6, the others in $CDCl_3$.

Table 4. Electronic Spectral Data of Compounds *III* and *IV* in Ethanol

Compound	λ_{max}/nm ($\varepsilon \cdot 10^{-2}$/(m^2 mol^{-1}))	
IIIa	254 (9.661)	320 (5.447)
IIIb	255 (11.112)	324 (6.582)
IIIc	255 (11.253)	326 (6.752)
IIId	253 (11.994)	326 (6.475)
IIIf	247 (10.263)	314 (4.775)
IIIg	254 (11.941)	322 (6.019)
IIIh	277 (10.051)	298 (7.809)
IVa	278 (12.363)	
IVb	304 (16.265)	
IVc	304 (15.573)	
IVd	300 (15.409)	
IVf	282 (10.393)	
IVg	308 (9.578)	
IVh	276 (9.989)	

EXPERIMENTAL

The course of the reaction was monitored by TLC on Silufol UV 254 (Kavalier, Votice), detection was carried out on Fluotest Universal (Quartzlampen, Hanau). Melting points were measured on Kofler apparatus Rapido 79/2106 (Wägetechnik) and elemental analyses were determined on instrument Model 1102 (Erba) and are presented together in Table 1. IR spectra were recorded on spectrometer SP 1000 (Unicam) and characteristic vibrations are collected in Table 2. ^{1}H NMR spectra were recorded on BS 567 apparatus (Tesla) with internal standard TMS and are presented in Table 3. Electronic spectra were recorded on spectrometer CARRY 118 in ethanol (Table 4).

2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (*I*)

2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thiophene (17.83 g; 0.1 mol) [4] was suspended in ethyl orthoformate (70 cm^3) and heated under reflux for 1.5 h. The solution thus formed was concentrated on a vacuum evaporator and then left to crystallize. The crystals were collected and washed with petroleum ether. After drying in a vacuum oven at room temperature the compound melts at 50.5—51.5 °C.

This compound is unstable in contact with air moisture and decomposes, which is accompanied by turning its colour to yellow. Yield = 19.2 g (81.9 %). IR spectrum (bromoform), $\tilde{\nu}$/cm^{-1}: 1215 ν(C—O), 1625 ν(C=N), 2210 ν(C≡N). ^{1}H NMR spectrum ($CDCl_3$), δ: 1.38 (t, 3H, CH_3), J = 7.5 Hz, 1.73—1.95 (m, 4H, CH_2), 2.53—2.74 (m, 4H, CH_2), 4.4 (q, 2H, CH_2), J = 7.5 Hz, 7.94 (s, 1H, CH).

Formamidines *IIa—IIe* and Cyclic Products *IIIf—IIIh*

Compound *I* (2.34 g; 0.01 mol) was dissolved in a minimum amount of ethanol (in case of compound *IIa* in benzene). Then the chosen nucleophile (0.01 mol) was added and the reaction mixture was either left standing or refluxed till the starting compound disappeared (reaction monitored by TLC). Then the mixture was concentrated to crystallization on a vacuum evaporator, crystals were collected and washed with petroleum ether and recrystallized.

In some cases the reaction under mentioned conditions proceeded following Scheme 1 to compounds *IIIf—IIIh* and then compound *II* could not be isolated.

3-Substituted 4-Imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-3,4-dihydropyrimidines *IIIa—IIId*

Compound *II* was dissolved in decalin (30 cm^3) (in case of *IIa* in ethanol) and refluxed till the starting compound disappeared (reaction monitored by TLC). Then the reaction mixture was cooled down and left to crystallize. The crystals were collected and washed with petroleum ether and recrystallized.

4-R-Amino-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidines *IVa—IVh*

Compound *III* (0.001 mol) dissolved in minimum amount of ethanol was heated with 5 drops of sodium hydroxide aqueous solution (15 %) to reflux. The course of the reaction was monitored by TLC. After compound *III* disappeared the reaction mixture was cooled down to crystallization (in case of compound *IVf* the mixture was poured into water). The separated crystals were recrystallized.

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Translated by M. Potáček