Chemistry of Heterocyclic Compounds, Vol. 34, No. 1, 1998

N-3-OXOALKYLAMIDES AND -THIOAMIDES IN SYNTHESIS OF HETEROCYCLIC COMPOUNDS. 3.* STUDY OF CYCLIZATION OF N-3-OXOALKYLTHIOAMIDES INTO 5,6-DIHYDROPYRIDINE-2(1H)-THIONES

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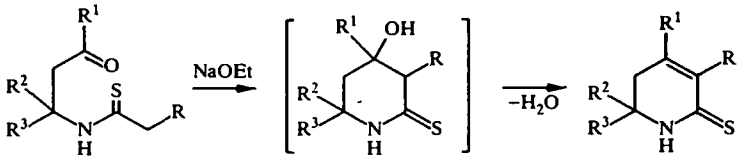
5,6-Dihydropyridine-2(1H)-thiones containing a hydrogen atom, aryl, or alkyl substituent in position 3 were obtained by cyclization of fatty acid N-3-oxoalkylthioamides with bases.

Our previously proposed method of synthesis of 5,6-dihydropyridin-2(1H)-ones based on N-3-oxoalkylamides has some limitations [2, 3]. In [2], we reported that the presence of a mobile hydrogen atom in the α-position with respect to the carbamoyl group is an obligatory condition for cyclization of N-3-oxoalkylamides with bases, making it impossible to obtain 3-unsubstituted and 3-alkyl-substituted 5,6-dihydropyridin-2(1H)-ones. The mobility of the hydrogen atom in the α-position to the thiocarbamoyl group is much higher than to the carbamoyl group, so that N-3-oxoalkylamides should be cyclized more easily than their oxygen analogs.

Using the method in [1], we obtained N-3-oxoalkylthioamides Ia-e. As a result of studying the reaction of compounds Ia-e with bases, we found that N-3-oxoalkylamides Ia-e are cyclized in 6% sodium ethylate solution at room temperature, forming 5,6-dihydropyridine-2(1H)-thiones IIa-e with high yields. Due to the higher mobility of the hydrogen atoms in the α-position with respect to the thiocarbamoyl group, the reaction takes place in softer conditions in comparison to the analogous N-3-oxoalkylamides [2]. It becomes possible to cyclize fatty acid N-3-oxoalkylthioamides and obtain not only 3-aryl- and 3-alkyl-substituted 5,6-dihydropyridine-2(1H)-thiones but also 5,6-dihydropyridyl-2(1H)-thiones unsubstituted in position 3.



Ia-e IIa-e

I, II a $R^1 = R^2 = R^3 = Me$, R = H; b $R^1 = R^2 = R^3 = R = Me$;
c $R^1 = R^2 = R^3 = Me$, R = Ph; d $R^1 = R^2 = Me$, $R^3 = R = H$;
e $R^1 = Me$, $R^2 = H$, $R^3 = R = Ph$

The rate of cyclization of N-3-oxoalkylthioamides, as in the case of N-3-oxoalkylamides [2, 3], is a function of the acidity of the α-position with respect to the thiocarbamoyl group and the effective bulk of the substituents in the N-3-oxoalkyl chain. A comparison of the time required for total conversion of compounds Ia and Ic, Ia and Id into the corresponding 5,6-dihydropyridine-2(1H)-thiones shows that an increase in the acidity of the α-position with respect to the thiocarbamoyl group and an increase in the effective bulk of the substituents in the α-position from the nitrogen atom increase the rate of cyclization of N-3-oxoalkylthioamides.

Compounds IIc and IIe were also obtained by back synthesis — by reaction of the corresponding 5,6-dihydropyridin-2(1H)-ones with P_2S_5. 3-Cyano-5,6-dihydropyridine-2(1H)-thiones IIf, g were obtained by the same method.

*See [1] for Communication 2.

Omsk State University, Omsk 644077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 73-76, January, 1998. Original article submitted April 7, 1997.

0009-3122/98/3401-0065$20.00

TABLE 1. Characteristics of Synthesized Compounds IIa-g

Compound	Empirical formula	Found, % / Calculated, % C	H	mp, *°C	IR spectrum, ν, cm⁻¹ ($CHCl_3$)	Reaction time, h	Yield (method), %
IIa*	$C_8H_{13}NS$	61,88 / 61,89	8,56 / 8,44	122...123	3370, 3200, 1650, 1495	2,5	93 (A)
IIb*	$C_9H_{15}NS$	63,86 / 63,86	8,92 / 8,93	149...150	3360, 1480, 1615, 1480	7,5	47 (A)
IIc†	$C_{14}H_{17}NS$	72,50 / 72,68	7,29 / 7,41	229...230	3370, 3200, 1625, 1480	0,3 —	87 (A) 85 (B)
IId*	$C_7H_{11}NS$	59,98 / 59,55	7,10 / 7,86	136...137	3385, 3200, 1635, 1495	48	40 (A)
IIe†	$C_{18}H_{17}NS$	77,02 / 77,39	6,35 / 6,14	169...170	3370, 1615, 1480	2,5 —	76 (A) 76 (B)
IIf†	$C_9H_{12}N_2S$	60,05 / 59,97	6,86 / 6,71	196...198	3360, 3155, 2220, 1610, 1495	—	82 (B)
IIg†	$C_{10}H_{14}N_2S$	62,10 / 61,82	7,16 / 7,26	166...168	2225, 1625, 1500	—	83 (B)

*From hexane.

†From ethanol.

TABLE 2. PMR, SSCC, J (Hz) of 5,6-Dihydropyridine-2(1H)-thiones

Compound	CH_2 H_a	CH_2 H_c	R	R^1	R^2	R^3	R^4
IIa	2,29		6,38, J^4 = 1,4	1,97, J^4 = 1,4	1,40		7,70
IIb	2,30		2,18	1,91	1,29		7,90
IIc	2,42		7,38...7,14	1,70	1,37		8,07
IId	2,10 J^3 = 12,4; J^2 = 17,5	2,26, J^3 = 6,0; J^2 = 17,5	6,28	1,91	3,71, J^3 = 12,4; 6,0; 6,4; J^3_{HNH} = = 1,4	1,32, J^3 = 6,4	8,10
IIe	2,98, J^2 = 12,5; J^3 = 10,5	2,68, J^2 = 12,5; J^3 = 7,0	7,49...7,21	1,81	4,86, J^3 = 10,5; 7,0; J^3_{HNH} = 1,8	7,49...7,21	7,92
IIf	2,60		—	2,42			8,13
IIg	2,60		—	2,35			3,57

TABLE 3. Mass Spectra of the Synthesized Compounds

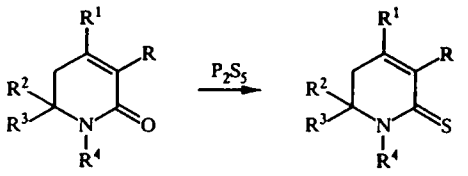
Compound	Relative intensity,* %
IIa	156 (11,0); 155 (100); 140 (86,3); 106 (35,0); 99 (9,5); 98 (24,6); 97 (8,2); 65 (6,5); 59 (7,5); 58 (20,1); 53 (8,4)
IIc	232 (24,3); 231 (98,9); 230 (100); 216 (32,7); 197 (18,2); 182 (13,2); 174 (16,3); 141 (18,6); 129 (12,7); 116 (14,0); 115 (33,3); 77 (12,9)
IIe	280 (22,6); 279 (100); 278 (99,4); 174 (21,1); 173 (15,6); 141 (20,0); 129 (16,9); 116 (19,9); 115 (46,6); 91 (24,0); 77 (22,4)
IIf	180 (89,8); 165 (100); 149 (20,3); 131 (23,9); 123 (14,8); 106 (59,3); 83 (24,1); 79 (18,9); 58 (23,2); 57 (24,6); 55 (19,0)
IIg	194 (75,3); 179 (96,2); 164 (13,7); 163 (66,7); 161 (22,4); 146 (13,0); 71 (13,2); 69 (15,0); 57 (16,5); 56 (100); 55 (20,8)

*The peaks of M^+ and the ten most intense ions are reported.

TABLE 4. Relative Intensity of the Peaks of Characteristic Fragmentary Ions in the Mass Spectra of the Synthesized Compounds

Compound	$[M]^{+\cdot}$	$[M-H]^+$	$[M-R2]^+$	$[M-R2-H_2S]^+$
IIa	155 (100)	—	140 (86,3)	106 (35,0)
IIc	231 (98,9)	230 (100)	216 (32,7)	182 (13,2)
IIe	279 (100)	278 (99,4)		246 (6,5)
IIf	180 (89,8)	179 (8,1)	165 (100)	131 (23,9)
IIIg	194 (75,3)	193 (6,0)	179 (96,2)	—

Compound	$[M-R^2-R^3CNH]^+$	$[M-R2-SH-R^3CNH]^+$	$[C_6H_5]^+$
IIa	98 (24,6)	65 (6,5)	—
IIc	174 (16,3)	141 (18,6)	77 (12,9)
IIe	174 (21,1)	141 (20,0)	77 (22,4)
IIf	123 (14,8)	—	—
IIIg	—	—	—



III a-d II c,e-g

IIIa, IIc $R^1 = R^2 = R^3 = Me$, $R^4 = H$, R = Ph; IIIb, IIe $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = R = Ph$; IIIc, IIf $R^1 = R^2 = R^3 = Me$, $R^4 = H$, R = CN; IIId, IIg $R^1 = R^2 = R^3 = R^4 = Me$, R = CN

The IR spectra of compounds IIa-f exhibit signals of stretching vibrations of a free and associated N−H bond in the region of 3385-3360 and 3200-3155 cm^{-1}. The signals in the 1650-1610 and 1500-1480 region corresponding to vibrations of the C=C bond and N−C=S group (thioamide II) in compounds IIa-g, and the signals at 2225-2220 cm^{-1} correspond to vibrations of the cyano group of compounds IIf, g.

The PMR spectra (Table 2) totally correspond to the structure of IIa-g.

The ^{13}C NMR spectrum of compound IIa recorded in a mixture of solvents $CDCl_3-CD_3OD$ at 190.2 (C=S), 144.6 ($C_{(4)}$), 124.7 ($C_{(3)}$), 52.9 ($C_{(6)}$), and 41.2 ppm ($C_{(5)}$) exhibit five signals of ^{13}C nuclei from atoms in the ring, signals of the 4-CH_3 group (22.4 ppm), and two magnetically equivalent groups at $C_{(6)}$ (27.2 ppm).

The direction of fragmentation under electron impact for 5,6-dihydropyridine-2(1H)-thiones is in agreement with the data for thioamides in [4]. Compounds IIa-g form a relatively stable $M^{+\cdot}$, so that $[M-H]^+$ and/or $[M-R_3]^+$ ions are formed as a result of decomposition. Their subsequent fragmentation leads to the formation of $[M-R^2-H_2S]^+$, $[M-R^2-R^3CNH]^+$, and $[M-R^2-SH-R^3CNH]^+$ ions in the mass spectra from compounds IIa-f and $[CH-C\equiv NCH_3]^+$ ions for compound IIg with *m/z* 56 (100%) (Tables 3 and 4).

Cyclization of N-3-oxoalkylthioamides with bases thus results in the formation of 4,6-dihydropyridine-2(1H)-thiones in soft conditions with high yields. The use of N-3-oxoalkylthioamides for formation of a 5,6-dihydropyridine ring removes the limitations characteristic of cyclization of N-3-oxoalkylamides and yields 5,6-dihydropyridine-2(1H)-thiones containing both an aryl and a hydrogen atom or alkyl substituent in position 3.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker-AC 200P and Tesla BS-587 (80 MHz) in $CDCl_3$, TMS internal standard. The IR spectra were recorded on a Specord IR-75 spectrometer in solutions of $CHCl_3$. The mass spectra were obtained on a

Finnigan MAT-112 spectrometer with direct introduction of the substance in the ion source and ionization energy of 70 eV. The evolution of the reaction and purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates with development with iodine vapors and UV light.

N-3-Oxoalkylamides Ia-e were obtained by the methods in [2, 3].

5,6-Dihydropyridine-2(1H)-thiones (IIa-e). A. Here 5 mmole of 1,3-oxoalkylthioacetamide Ia-e was added to 40 ml of a 6% solution of sodium ethylate in ethanol. The reaction mixture was stirred in an inert gas current until the starting compound disappeared (TLC monitoring), then neutralized with 10% HCl. The solvent was distilled off and the residue was extracted with benzene (2 × 20 ml). After distillation of the solvent, the compounds were purified by recrystallization.

5,6-Dihydropyridine-2(1H)-thiones (IIc, d-g). B. Here 4.6 mmole of 5,6-dihydropyridine-2(1H)one IIIa-d was dissolved in 30 ml of absolute toluene, and 1.00 g (4.5 mmole) of P_2S_5 was added by portions to the boiling solution. The reaction mixture was boiled until the starting compound disappeared (TLC monitoring), the hot solution was poured off the sediment, the solvent was distilled off, and the residue was purified by recrystallization.

The research received financial support from the Russian Fund for Fundamental Research (Project Code 97-03-33119a).

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