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SYNTHESIS OF 3-S-HETARYL-SUBSTITUTED PYRIDIN-2(1H)-ONES AND 5,6-DIHYDROPYRIDIN-2(1H)-ONES*

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A method has been developed for the synthesis of 3-S-hetaryl-substituted pyridin-2(1H)-ones and 5,6-dihydropyridin-2(1H)-ones based on the base catalyzed cyclization of N-(3-oxoalkyl)- and N-(3-oxoalkenyl)amides which contain a divalent sulfur atom in an α-position to a carbamoyl group and bound to the heterocycle.

Keywords: 5,6-dihydropyridin-2(1H)-ones, N-(3-oxoalkenyl)amides, N-(3-oxoalkyl)amides, pyridin-2(1H)-ones, intramolecular cyclization.

We have previously reported that N-(3-oxoalkenyl)- and N-(3-oxoalkyl)amides containing a mobile hydrogen atom in an α-position to the carbamoyl group can undergo an aldol type intramolecular ring closure to give pyridin-2(1H)-ones [1] or their hydrogenated derivatives [2]. In order to increase the acidity, various acceptors including a pyridine ring [3, 4], triphenylphosphonium group [5, 6], halogen atom [7], and a tosyl [8] or aryl [9] substituent were introduced to the α-carbamoyl position. It is possible to introduce a divalent sulfur atom in order to stabilize the carbanion and so increase the acidity at the α-carbamoyl position. In our case, this can be achieved by the nucleophilic substitution of the halogen in N-(3-oxoalkenyl)- and N-(3-oxoalkyl)-chloroacetamides by a thio group. At the same time the use of thiophenol and thiols in the synthesis is not without the drawback of an unpleasant odor. The introduction of a divalent sulfur atom in the molecule is possible by the S-alkylation of cyclic thioamides, thiocarbamates, or thiourea. The compounds are generally crystalline and do not have an objectionable odor. We have previously reported such a possible route [10].

With the aim of studying the cyclization of N-(3-oxoalkenyl)- and N-(3-oxoalkyl)amides containing a divalent sulfur atom in an α-carbamoyl position we have prepared the compounds **4a**, **5a-e** by treating the chloroacetamides **1**, **2** (synthesized by known methods [1, 9]) with the thio derivatives **3a-e**. The reactions were carried out in DMF at room temperature in the presence of potassium carbonate and potassium iodide. The completion of the reaction was monitored by TLC. The yields of compounds **4a** and **5a-e** were 54-88% (Table 1).

It was found that cyclization of compounds **5a**,**d** occurs even at room temperature over 2-3 h with the action of sodium ethylate in ethanol to give the 5,6-dihydropyridin-2(1H)-ones **7a**,**d** in 80-90% yield. Cyclization of compounds **5b**,**c**,**e** occurs more slowly and it is necessary to carry out the reaction with heating. The yield of compounds **7b**,**c**,**e** is 57-73% (Table 1). It should be noted that cyclization of compound **4a** occurs

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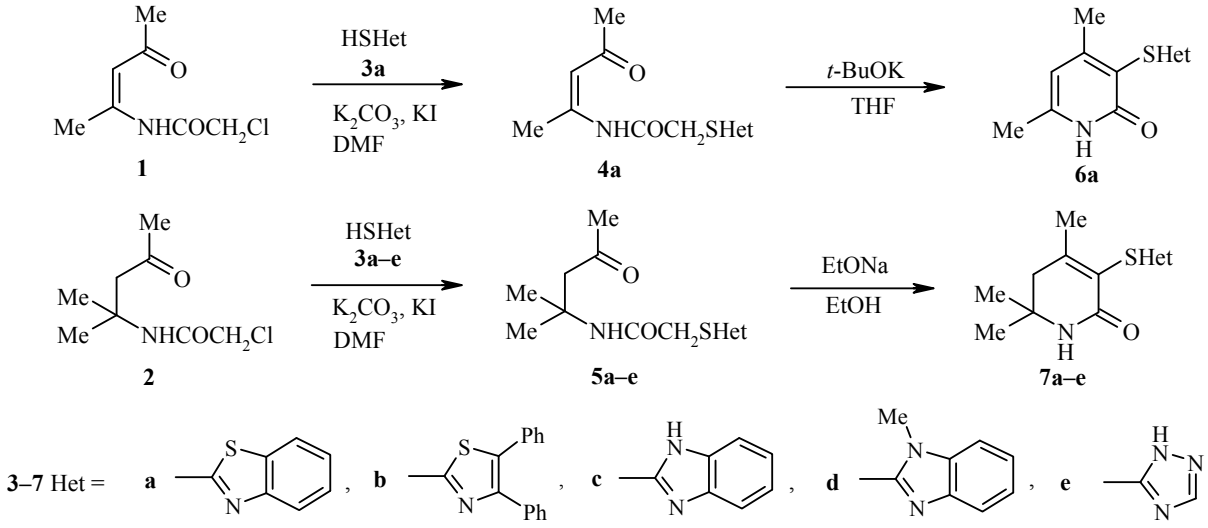
under analogous conditions to yield a hard to separate mixture of products, evidently as a result of the alcoholysis of the starting compound. The pyridin-2(1H)-one **6a** was prepared in 88% yield by carrying out the reaction in anhydrous THF with the use of potassium *tert*-butylate as base.



The IR spectra of compounds **6a** and **7a-e** show the absence of absorption bands for the carbonyl group. The ^{1}H and ^{13}C NMR spectra confirm the structures of compounds **6a** and **7a-e** (Tables 2 and 3).

TABLE 1. Characteristics and Conditions for Preparing Compounds **4-7**

Compound	Empirical formula	Found, % / Calculated, %			Reaction time, h	Reaction T, °C	mp, °C*	Yield, %
		C	H	N				
4a	$C_{14}H_{14}N_2O_2S_2$	54.67 / 54.88	4.66 / 4.61	9.07 / 9.14	72	25	142-143	78
5a	$C_{15}H_{18}N_2O_2S$	55.62 / 55.87	5.56 / 5.63	8.62 / 8.69	30	25	71-72	80
5b	$C_{23}H_{24}N_2O_2S$	65.18 / 65.06	5.77 / 5.70	6.64 / 6.60	30	25	175-176	88
5c	$C_{15}H_{19}N_3O_2S$	58.71 / 58.99	6.35 / 6.27	13.68 / 13.76	72	25	175-176	54
5d	$C_{16}H_{21}N_3O_2S$	60.35 / 60.16	6.58 / 6.63	13.07 / 13.16	72	25	97-98	64
5e	$C_{10}H_{16}N_4O_2S$	46.69 / 46.86	6.38 / 6.29	21.69 / 21.86	30	25	75-76	62
6a	$C_{14}H_{12}N_2OS_2$	58.43 / 58.31	4.25 / 4.19	9.62 / 9.71	1	25	> 245	88
7a	$C_{15}H_{16}N_2OS_2$	59.35 / 59.18	5.41 / 5.30	9.14 / 9.20	2	25	180-181	79
7b	$C_{23}H_{22}N_2OS_2$	67.82 / 67.95	5.34 / 5.45	6.95 / 6.89	3	75-80	244-245	68
7c	$C_{15}H_{17}N_3OS$	62.53 / 62.69	5.88 / 5.96	14.51 / 14.62	1	75-80	232-233	73
7d	$C_{16}H_{19}N_3OS$	63.92 / 63.76	6.42 / 6.35	13.86 / 13.94	3	25	202-203	90
7e	$C_{10}H_{14}N_4OS$	50.54 / 50.40	5.81 / 5.92	23.34 / 23.51	2	75-80	243-244	57

* Solvents: 70% ethanol (compounds **4a**, **5a-d**), 40:70 mixture of ethyl acetate and petroleum ether (compound **5e**), ethanol (compound **6a**) or 50% ethanol (compounds **7a-e**).

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **4–7**

Compound	IR spectrum, ν, cm^{-1}*		^{1}H NMR spectrum, δ, ppm (*J*, Hz)*^{2}
	(NH) C=O	N–C=O	
4a	(3330) 1680	1615	2.13 (3H, s, H-4); 2.37 (3H, d, ^4J = 1.0, =C–CH$_3$); 4.19 (2H, s, S–CH$_2$); 5.35–5.37 (1H, d, =CH); 7.27-7.46 (2H, d, Ar); 7.72-7.92 (2H, d, Ar); 12.84 (1H, br. s, NH)
5a	(3270) 1710	1645	1.36 (6H, s, 1-(CH$_3$)$_2$); 2.05 (3H, s, H-4); 2.94 (2H, s, CH$_3$–C(O)–CH$_2$); 3.86 (2H, s, S–CH$_2$); 7.29-7.44 (2H, d, Ar); 7.73 (1H, br. s, NH); 7.76-7.87 (2H, d, Ar)
5b	(3280) 1700	1650	1.36 (6H, s, 1-(CH$_3$)$_2$); 2.04 (3H, s, H-4); 2.95 (2H, s, CH$_3$–C(O)–CH$_2$); 3.57 (2H, s, S–CH$_2$); 7.19–7.67 (10H, d, 2C$_6$H$_5$); 7.96 (1H, br. s, NH)
5c	(3270) 1710	1665	1.34 (6H, s, 1-(CH$_3$)$_2$); 2.03 (3H, s, H-4); 2.95 (2H, s, CH$_3$–C(O)–CH$_2$); 3.86 (2H, s, S–CH$_2$); 7.15–7.22 (2H, d, Ar); 7.43–7.50 (2H, d, Ar)
5d	(3300) 1710	1675	1.35 (6H, s, 1-(CH$_3$)$_2$); 2.05 (3H, s, H-4); 2.95 (2H, s, CH$_3$–C(O)–CH$_2$); 3.70 (3H, s, N–CH$_3$); 3.82 (2H, s, S–CH$_2$); 7.20-7.31 (2H, d, Ar); 7.56-7.63 (2H, d, Ar); 8.68 (1H, br. s, NH)
5e	(3175) 1710	1665	1.36 (6H, s, 1-(CH$_3$)$_2$); 2.08 (3H, s, H-4); 2.94 (2H, s, CH$_3$–C(O)–CH$_2$); 3.68 (2H, s, S–CH$_2$); 7.48 (1H, s, CH triazolyl); 8.18 (1H, br. s, NH)
6a	(3150)	1615	2.25 (3H, s, 6-CH$_3$); 2.36 (3H, s, 4-CH$_3$); 6.21 (1H, s, H-5); 7.27–7.47 (2H, d, Ar); 7.76-7.93 (2H, d, Ar); 12.12 (1H, br. s, NH)
7a	(3190)	1655	1.37 (6H, s, 6-(CH$_3$)$_2$); 2.28 (3H, s, 4-CH$_3$); 2.57 (2H, s, CH$_2$); 6.08 (1H, br. s, NH); 7.23-7.43 (2H, d, Ar); 7.67-7.91 (2H, d, Ar)
7b	(3145)	1650	1.26 (6H, s, 6-(CH$_3$)$_2$); 2.16 (3H, s, 4-CH$_3$); 2.46 (2H, s, CH$_2$); 7.11-7.52 (10H, d, 2C$_6$H$_5$); 7.63 (1H, br. s, NH)
7c	(3255)	1650	1.30 (6H, s, 6-(CH$_3$)$_2$); 2.27 (3H, s, 4-CH$_3$); 2.62 (2H, s, CH$_2$); 7.10-7.19 (2H, d, Ar); 7.37–7.48 (2H, d, Ar); 7.56 (1H, br. s, NH)
7d	(3175)	1650	1.26 (6H, s, 6-(CH$_3$)$_2$); 2.30 (3H, s, 4-CH$_3$); 2.48 (2H, s, CH$_2$); 3.87 (3H, s, N–CH$_3$); 5.93 (1H, br. s, NH); 7.14-7.27 (2H, d, Ar); 7.58-7.62 (2H, d, Ar)
7e	(3130)	1640	1.22 (6H, s, 6-(CH$_3$)$_2$); 2.08 (3H, s, 4-CH$_3$); 2.44 (2H, s, CH$_2$); 7.57 (1H, s, CH triazolyl); 8.28 (1H, br. s, NH)

* IR spectra were recorded for KBr tablets (compounds **4a**, **5a**,**b**,**d**,**e**, **6a, 7a**,**b**,**d**,**e**) or CHCl$_3$ (compounds **5c** and **7c**).

*^{2} ^{1}H NMR spectra were recorded in CDCl$_3$ (compounds **4a**, **5a**,**b**,**d**,**e**, **7a**,**b**), CD$_3$OD (compounds **5c** and **7c**) or DMSO-d$_6$ (compounds **6a**, **7d**,**e**).

TABLE 3. ^{13}C NMR Spectra and Mass Spectra of Compounds **4–7**

Compound	^{13}C NMR spectrum, δ, ppm*	Mass spectrum, *m/z* $[M]^+$
4a	21.76 (1-CH_3); 30.46 (C-4); 37.84 (CH_2); 106.61 (C-2); 121.01, 121.86, 124.43, 126.00, 135.65, 152.77 (Ar); 154.03 (C-1); 164.16 (C–S benzothiazolyl); 167.28 (NCO); 199.39 (C=O)	—
5a	27.15 (1-(CH_3)$_2$); 31.51 (C-4); 36.99 (CH_2–S); 50.81 (C-2); 52.23 (C-1); 121.19, 121.24, 124.71, 126.33, 135.43, 152.27 (Ar); 160.98 (C–S benzothiazolyl); 167.61 (NCO); 207.30 (C-3)	322
5b	27.08 (1-(CH_3)$_2$); 31.56 (C-4); 37.97 (CH_2–S); 50.95 (C-2); 52.46 (C-1); 127.66, 128.43, 139.85 ($2C_6H_5$); 169.61 (NCO); 208.41 (C-3)	—
5c	27.51 (1-(CH_3)$_2$); 31.67 (C-4); 37.04 (CH_2-S); 51.67 (C-2); 53.56 (C-1); 123.57 (Ar); 151.29 (C–S benzimidazolyl); 170.37 (NCO); 209.78 (C-3)	305
5d	26.97 (1-(CH_3)$_2$); 30.13 (N–CH_3); 31.48 (C-4); 35.76 (CH_2–S); 50.89 (C-2); 52.04 (C-1); 108.66, 117.71, 122.18, 136.76, 142.44 (Ar); 152.18 (C–S benzimidazolyl); 168.40 (NCO); 207.31 (C-3)	319
5e	27.12 (1-(CH_3)$_2$); 31.64 (C-4); 36.24 (CH_2–S); 50.75 (C-2); 52.52 (C-1); 120.00 (CH triazolyl); 156.90 (C–S triazolyl); 168.77 (NCO); 208.06 (C-3)	256
6a	18.58 (6-CH_3); 21.38 (4-CH_3); 107.89 (C-5); 113.72 (C-3); 121.04, 121.59, 124.05, 126.21, 134.71 (Ar); 148.79 (C-6); 153.87 (C-4); 160.16 (C–S benzothiazolyl); 161.34 (Ar); 169.74 (C-2)	288
7a	23.73 (4-CH_3); 29.05 (6-(CH_3)$_2$); 45.48 (C-5); 50.67 (C-6); 120.72 (C-3); 121.08, 121.82, 124.08, 125.93, 135.45 (Ar); 153.72 (C-4); 161.59 (C–S benzthiazolyl); 162.74 (Ar); 167.62 (C-2)	304
7b	23.04 (4-CH_3); 28.16 (6-(CH_3)$_2$); 44.68 (C-5); 49.93 (C-6); 120.25 (C-3); 126.34, 126.72, 127.81, 127.96, 128.06, 128.65, 130.91, 134.99, 136.92, 140.11 (Ar); 156.33 (C-4); 162.57 (C-2)	—
7c	22.41 (4-CH_3); 27.40 (6-(CH_3)$_2$); 44.57 (C-5); 50.12 (C-6); 118.11 (C-3); 121.86 (Ar); 149.79 (C-4); 161.98 (C–S benzoimidazolyl); 163.86 (C-2)	287
7d	23.61 (4-CH_3); 28.71 (6-(CH_3)$_2$); 30.71 (N–CH_3); 45.30 (C-5); 50.59 (C-6); 108.86, 118.94 (Ar); 120.57 (C-3); 121.58, 121.98, 136.43, 143.42 (Ar); 149.92 (C-4); 157.50 (benzoimidazolyl); 163.24 (C-2)	301
7e	23.08 (4-CH_3); 28.30 (6-(CH_3)$_2$); 44.63 (C-5); 49.89 (C-6); 109.56 (C-3); 144.34 (CH triazolyl); 156.92 (C–S triazolyl); 162.33 (C-2)	238

* ^{13}C spectra were recorded in $CDCl_3$ (for compounds **4a**, **5a**,**b**,**d**,**e**, **7a**,**b**), CD_3OD (for compounds **5c** and **7c**) or DMSO-d_6 (compounds **6a**, **7d**,**e**).

Hence we have developed a method for the preparation of pyridin-2(1H)-ones and 5,6-dihydropyridin-2(1H)-ones which contain a divalent sulfur atom at position C(3) and bound to a heterocycle. It was found that cyclic thioureas and thiocarbamates can be successfully used to increase the acidity at the α-carbamoyl position.

EXPERIMENTAL

IR spectra were recorded on an Infralum FT-801 spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker DRX-400 instrument (400 and 100 MHz respectively) with TMS as internal standard. Mass spectra were obtained on an Agilent 5973N instrument (ionization energy 70 eV, evaporator temperature 230-250ºC). Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on Sorbfil UV-254 plates and revealed using iodine vapor or UV light. Melting points were determined on a Koffler stage.

Compounds **1** and **2** were synthesized by acylation of the corresponding amino ketone [9] and enamino ketone [1] using monochloroacetic acid chloride. With the exception of the commercially available mercaptobenzothiazole **3a** the starting thiocarbamates and thioureas were prepared by a known method: **3b** [11], **3c**,**d** [12], or **3e** [13].

N-(1,1-Dimethyl-3-oxobutyl)-2-(hetarylsulfanyl)acetamides 5a-e (General Method). A solution of the chloroacetamide **2** (0.192 g, 1.0 mmol), the corresponding thiocarbamate or thiourea **3a-e** (1.0 mmol), anhydrous K_2CO_3 (0.138 g, 1.0 mmol), and KI (0.017 g, 0.1 mmol) in absolute DMF (2 ml) was stirred at room temperature for 30-72 h while the reaction was monitored by TLC. The reaction product was diluted with water (10 ml), neutralized with 10% HCl solution, and the precipitate was filtered off. The compound was recrystallized from 70% ethanol. Compound **5e** was recrystallized from a 40:70 mixture of ethyl acetate and petroleum ether.

2-(1,3-Benzothiazol-2-ylsulfanyl)-N-(1-methyl-3-oxobut-1-en-1-yl)acetamide (4a) was prepared similarly to compounds **5a-e.**

3-(1,3-Benzothiazol-2-ylsulfanyl)-4,6-dimethylpyridin-2(1H)-one (6a). Potassium *tert*-butylate (0.17 g, 1.5 mmol) was added with stirring and cooling in ice to a solution of the acetamide **4a** (0.306 g, 1.0 mmol) in anhydrous THF (5 ml) and stirred for 10-15 min. Cooling was removed and stirring was continued at room temperature for 1 h (TLC monitoring). Solvent was removed *in vacuo* and the reaction product was treated with water, neutralized with a 10% solution of HCl, and the precipitate formed was filtered off. The compound was recrystallized from ethanol.

3-(Hetarylsulfanyl)-4,6,6,-trimethyl-5,6-dihydropyridin-2(1H)-ones (7a-e) (General Method). A solution of sodium ethylate was prepared by dissolving sodium (1 mmol) in absolute ethanol (3 ml) and added dropwise with stirring to a solution of compound **5a-e** (1 mmol) in absolute ethanol (3 ml). The reaction product was stirred for 2-3 h at room temperature (**7a**,**d**) or refluxed for 1-3 h (**7b**,**c**,**e**) and then neutralized with 10% HCl solution. Solvent was evaporated *in vacuo* and the residue was washed with water (10 ml) and filtered off. The compound was recrystallized from 50% ethanol.

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