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A New Route to 5,6-Dihydropyridine-2(1H)-thiones

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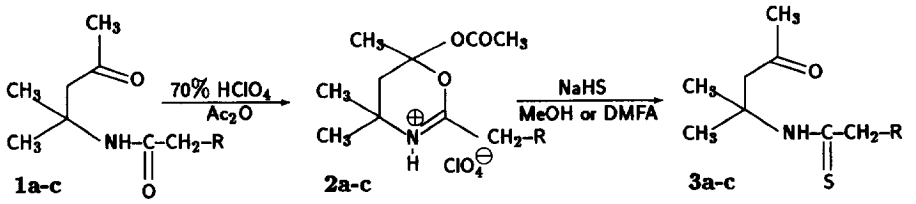
Abstract: New 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorates **2** were synthesized by cyclization of N-3-oxoalkylamides **1**. The reaction of **2** with sodium hydrosulfide in methanol or dimethylformamide results in the formation of unknown N-3-oxoalkylthioamides **3**. New 5,6-dihydropyridine-2(1H)-thiones **4** were prepared by cyclization of **3**.

We have earlier reported[1] the cyclization of N-3-oxoalkylarylacetamides in the presence of bases into 3-aryl-5,6-dihydropyridine-2(1H)-ones, which have attracted growing attention as biological active compounds or precursors for the synthesis of the analogues of the alkaloids.[2]

The proposed method may be used for the synthesis various dihydropyridine-2(1H)-ones because the starting N-3-oxoalkylamides are readily available.[3 – 6] However, it should be noted that the obligatory presence of active hydrogen atoms at the α-carbamoyl position of the starting material did not allow 3-unsubstituted or 3-alkyl-substituted 5,6-dihydropyridine-2(1H)-ones to be synthesized. The replacement of the carbamoyl group to the thiocarbamoyl may be one way to solve this problem because of the higher activity of the hydrogen atoms at the α-thiocarbamoyl position. It should however be emphasised that there were no information about the synthesis of the N-3-oxoalkylthioamides till now.

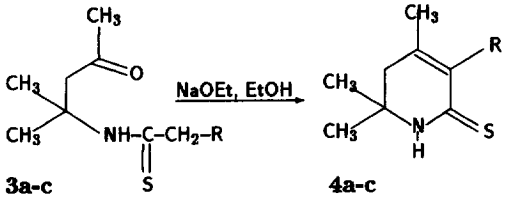
We have developed an original method to convert N-3-oxoalkylamides into N-3-oxoalkylthioamides. Interaction of N-3-oxoalkylamides **1a-c**, obtained according to the described procedures[3,6] with 70% perchloric acid in acetic anhydride, gave unknown 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorates **2a-c**.[7] These were converted into N-3-oxoalkylthioamides **3a-c** [8] in high yields under treatment with sodium hydrosulfide solution in methanol or dimethylformamide (Scheme 1).



a: R = H; **b:** R = Ph; **c:** R = CH_3.

Scheme 1

The cyclization of **3a-c** in the presence of NaOEt gave 5,6-dihydropyridine-2(1H)-thiones **4a-c**.[9] It should be noted that this route allowed both 3-aryl- and 3-alkyl-substituted 5,6-dihydropyridine-2(1H)-thiones to be obtained (Scheme 2), see Table 1.



Scheme 2

Table 1.

Sub.	Reagents and conditions	τ, h	Yield, %	M.p., ^{0}C
2a	70% $HClO_4$, Ac_2O	1	70.0	95–97 ($MeCN/Et_2O$)
2b	70% $HClO_4$, Ac_2O	1	89.0	125–126 ($MeCN/Et_2O$)
2c	70% $HClO_4$, Ac_2O	1	80.0	84–85 ($MeCN/Et_2O$)
3a	**2a**, NaHS in MeOH	48	75.3	85–86 (hexane)
3b	**2b**, NaHS in MeOH	48	62.0	69–70 (hexane)
3c	**2c**, NaHS in MeOH	48	75.0	51–52 (hexane)
	2c, NaHS in DMFA	6	98.7	51–52 (hexane)
4a	**3a**, 6% NaOEt/EtOH	2.5	93.0	122–123 (hexane)
4b	**3b**, 6% NaOEt/EtOH	0.33	87.0	229–230 (hexane)
4c	**3c**, 6% NaOEt/EtOH	7.5	46.8	149–150 (hexane)

IR and ^1H NMR specrtoscopic data and elemental analysis of the obtained substances are entirely consistent with the assigned structures. The alternative synthesis of 5,6-dihydropyridine-2(1H)-thione **4b** was also carried out from the related 5,6-dihydropyridine-2(1H)-one[1] and P_2S_5.

So, it have been shown that new 5,6-dihydropyridine-2(1H)-thiones containing both acceptor and hydrogen or alkyl radicals at the position 3 may be synthesized by this method. When taking into account availability of the starting N-3-oxoalkylamides this route to the pyridine ring being formed the basis of the many biological active compounds[10] may be interesting.

References and notes

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7. Data for **2a**: IR ($CHCl_3$, cm^{-1}): 3230 (–NH=); 1780 (–COO–); 1685 (–C=NH–); 1120 (ClO_4). ^1H NMR (200 MHz, D_6–DMSO): 6.19 (brs, 1 H, NH); 2.63 (d, 1 H, ^2J = 16.8 Hz, 5-He); 2.15 (d, 1 H, ^2J = 16.8 Hz, 5-Ha); 2.27 (s, 3 H, 2-CH_3); 2.02 s, 3 H, CH_3–CO–); 1.84 (s, 3 H, 6-CH_3); 1.37 (s, 3 H, 4-CH_3e); 1.32 (s, 3 H, 4-CH_3a).
   Data for **2b**: IR ($CHCl_3$, cm^{-1}): 3200 (=NH–); 1770 (–COO–); 1680 (–C=NH–); 1130 ClO_4). ^1H NMR (200 MHz, D_6–DMSO): 7.30 (m, 5 H, Ph); 3.89 (s, 2 H, –CH_2–Ph); 2.65 d, 1 H, ^2J = 14.6 Hz, 5-He); 2.17 (d, 1 H, ^2J = 14.6 Hz, 5-Ha); 1.86 (s, 3 H, CH_3–CO–); 1.79 (s, 3 H, 6-CH_3); 1.38 (s, 6 H, 4-$(CH_3)_2$).
   Data for **2c**: IR ($CHCl_3$, cm^{-1}): 3233 (–NH=); 1773 (–COO–); 1686 (–C=NH–). ^1H NMR (200 MHz, CD_3CN): 2.45 (d, 1 H, ^2J = 15.2 Hz, 5-He); 2.35 (q, 2 H, ^3J = 7.5 Hz, –CH_2–CH_3); 2.31 (d, 1 H, ^2J = 15.2 Hz, 5-Ha); 1.77 (s, 3 H, 6-CH_3–CO–); 1.65 (s, 3 H, 6-CH_3); 1.21 (s, 3 H, 4-CH_3e); 1.14 (s, 3 H, 4-CH_3a); 1.01 (t, 3 H, ^3J = 7.5 Hz, –CH_2–CH_3).
8. Data for **3a**: IR ($CHCl_3$, cm^{-1}): 3390 (NH); 1710 (CO); 1420 (CS–N); 1170 (C=S). ^1H NMR (200 MHz, $CDCl_3$): 9.42 (brs, 1 H, NH); 3.37 (s, 2 H, -CH_2–); 2 30 (s, 3 H, CH_3–CS–); 1.90 (s, 3 H, 3-CH_3); 1.40 (s, 6 H, 1-$(CH_3)_2$). M^+ = 173.0

Data for **3b**: IR ($CHCl_3$, cm^{-1}): 3350 (NH); 1720 (CO); 1430 (-N-C=S); 1160 (C=S). ^1H NMR (200 MHz, $CDCl_3$): 9.67 (brs, 1 H, NH); 7.25 (m, 6 H, Ph); 3.81 (s, 2 H, $-CH_2-Ph$); 3.34 (s, 2 H, $-CH_2-$); 1.92 (s, 3 H, 3-CH_3); 1.43 (s, 6 H, 2*CH_3). $M^+ = 249.0$

Data for **3c**: IR ($CHCl_3$, cm^{-1}): 3380 (NH); 1713 (CO); 1380 (-N-C=S); 1160 (C=S). ^1H NMR (200 MHz, $CDCl_3$): 5.90 (brs, 1 H, NH); 2.90 (s, 2 H, $-CH_2-$); 2.09 (q, 2 H, $^3J = 7.5$ Hz, $\underline{-CH_2}-CH_3$); 2.08 (s, 3 H, $CH_3-C=O$); 1.35 (s, 6 H, 2*CH_3); 1.05 (t, 3 H, $^3J = 7.5$ Hz, $-CH_2-\underline{CH_3}$).

9. Data for **4a**: IR ($CHCl_3$, cm^{-1}): 3380 (NH); 1505 (-N-C=S); 1180 (C=S). ^1H NMR (200 MHz, $CDCl_3$): 7.70 (brs, 1 H, NH); 6.38 (m, 1 H, $^4J_{HCH_3} = 1.2$ Hz, 3-H); 2.29 (s, 2 H, 5-H); 1.97 (d, 3 H, $^4J_{HCH_3} = 1.2$ Hz, 4-CH_3); 1.40 (s, 6 H, 6-$(CH_3)_2$). $M^+ = 155.0$

Data for **4b**: IR ($CHCl_3$, cm^{-1}): 3380 (NH); 1495 (-N-C=S); 1140 (C=S). ^1H NMR (200 MHz, $CDCl_3$): 8.07 (brs, 1 H, NH); 7.32 (m, 5 H, 3-Ph); 2.42 (s, 2 H, 5-H); 1.70 (s, 3 H, 4-CH_3); 1.37 (s, 6 H, 6-$(CH_3)_2$). $M^+ = 231.0$

Data for **4c**: IR ($CHCl_3$, cm^{-1}): 3346 (NH); 1480 (-N-C=S); 1120 (C=S). ^1H HMR (200 MHz, $CDCl_3$): 7.90 (brs, 1 H, NH); 2.30 (s, 2 H, 5-H); 2.18 (q, 3 H, $^4J = 0.9$ Hz, 3-CH_3); 1.91 (q, 3 H, $^4J = 0.9$ Hz, 4-CH_3); 1.29 (s, 6 H, 6-$(CH_3)_2$).

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