Synthesis and some properties of 4-alkyl-5-cyano-6-mercapto-3,4-dihydropyridin-2(1*H*)-ones

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Condensation of propionic (or acetic) aldehyde, cyanothioacetamide, Meldrum's acid, and *N*-methylmorpholine occurs *via* the intermediate formation of the corresponding Michael adducts and yields 4-alkyl-5-cyano-6-mercapto-3,4-dihydropyridin-2(1*H*)-ones. The oxidation of the reaction products with DMSO and their alkylation were studied.

Key words: condensation, aliphatic aldehydes, Meldrum's acid, Michael adducts, cyclization, oxidation, alkylation.

Meldrum's acid and its derivatives have been used successfully for the synthesis of hetaryl-substituted piperidin-2(1*H*)-ones,[1] 4-aryl-3,4-dihydropyridin-2(1*H*)-ones,[2] and hexahydroquinolin-2-one derivatives[3]. Recently[4] we have shown that the adducts resulting from the addition of Meldrum's acid to arylmethylenecyanothioacetamides can be cyclized to 4-aryl-5-cyano-6-mercapto-3,4-dihydropyridin-2(1*H*)-ones. However, 4-alkyl-3-cyano-3,4-dihydropyridin-2(1*H*)-ones, which would certainly be promising synthons for the synthesis of biologically active compounds,[5] have not yet been obtained.

In this work, we studied the condensation of aliphatic aldehydes (**1**), cyanothioacetamide (**2**), and Meldrum's acid (**3**) in ethanol at 20 °C in the presence of excess *N*-methylmorpholine (Scheme 1). It was found that this reaction yields Michael adducts, which were isolated as *N*-methylmorpholinium salts (**4**). Their structures are in agreement with the data of spectroscopic studies (see Experimental). Up to now, adducts of this type have been known only for R = Ar, Het.[6]

Refluxing compound **4a** in ethanol gives *N*-methylmorpholinium 3-cyano-4-ethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (**5**) (method *A*); this product can also be obtained by refluxing equimolar amounts of propionic aldehyde (**1a**), cyanothioacetamide (**2**), Meldrum's acid (**3**), and an excess of *N*-methylmorpholine in ethanol for 3 h (method *B*).

Treatment of compound **5** with dilute hydrochloric acid yields 5-cyano-4-ethyl-6-mercapto-3,4-dihydropyridin-2(1*H*)-one (**6a**) (method *C*). Compounds **6a,c**, which exist in DMSO solutions as mixtures of prototropic tautomers **6A** and **6B** as indicated by the data of ^{1}H NMR spectroscopy (see Experimental), can also be obtained without isolation of the intermediate products (method *D*). The reaction of aldehyde **1b** with cyanothioacetamide **2** and Meldrum's acid **3** under similar conditions affords a complex mixture of products; we were not able to isolate compound **6b** from this mixture.

To confirm the structures of compounds **6a,c**, 5-cyano-6-mercapto-4-methyl-3,4-dihydropyridin-2(1*H*)-one (**6c**) was oxidized by heating in DMSO to substituted pyridone **7**, which we have obtained previously by the reaction of ethyl acetoacetate enamine with cyanothioacetamide.[7]

Alkylation of salts **5** with halides **8** gave sulfides **10** (method *E*); these compounds were also synthesized by the reaction of mercaptans **6** with halides **8** in a basic medium (method *F*). The alkylation of pyridones **7** with halides **9** in DMF in the presence of an aqueous solution of KOH also occurs at the sulfur atom, despite the presence of other nucleophilic centers (C=O, NH) in the molecule of **7**. The use of an excess of the base in this reaction results in the formation of substituted thieno[2,3-*b*]pyridines **12**, whose structure is not at variance with the results of physicochemical and spectral studies (Tables 1 and 2).

Experimental

^{1}H NMR spectra were recorded on a Bruker-WP-100 SY spectrometer (100 MHz) in DMSO-d_6 using tetramethylsilane as the standard. IR spectra were obtained on an IKS-29 spectrophotometer in Vaseline oil. The individuality of the compounds was checked by TLC on Silufol UV-254 plates using the acetone—heptane system (3 : 5).

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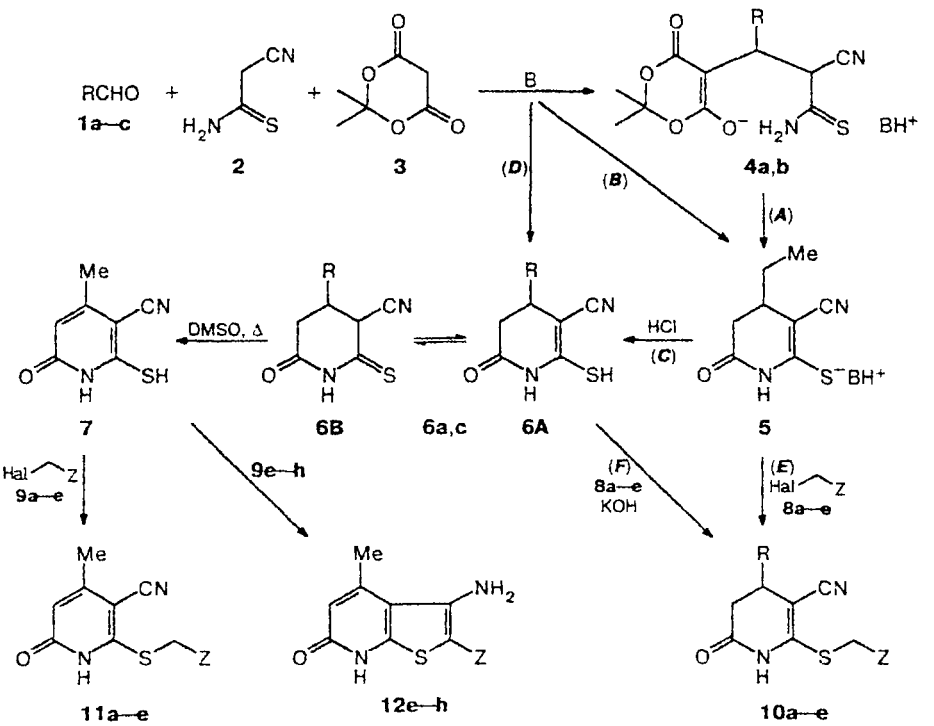
Scheme 1



B = *N*-methylmorpholine

1, **4**, **6**: R = Et (**a**), $CHMe_2$ (**b**), Me (**c**)

8, **10**	Hal	Z	R
a	I	H	Me
b	I	H	Et
c	I	Me	Et
d	Cl	COOEt	Et
e	Br	4-$C_6H_5C_6H_4CO$	Me

9, **11**, **12**	Hal	Z
a	Cl	$COOCH_2Ph$
b	Cl	COOMe
c	Cl	Ph
d	Cl	4-BrC_6H_4NHCO

	Hal	Z
e	Br	3-BrC_6H_4CO
f	Br	4-$NO_2C_6H_4CO$
g	Br	3,4-$Cl_2C_6H_3CO$
h	Br	3-Cumarinyl-carbonyl

***N*-Methylmorpholinium 2,2-dimethyl-6-oxo-5-(1-cyano-1-thiocarbamoylbut-2-yl)-1,3-dioxacyclohex-4-en-4-olate (4a).** *N*-Methylmorpholine (12 mmol) was added with stirring at 20 °C to a suspension of propionic aldehyde (**1a**) (10 mmol), cyanothioacetamide (**2**) (10 mmol), and Meldrum's acid (**3**) (10 mmol) in 15 mL of ethanol. After 3 h, the precipitate was filtered off and washed with acetone. Yield 3.2 g (83%), m.p. 133—135 °C. Found (%): C, 53.13; H, 6.91; N, 10.77; S, 8.15. $C_{17}H_{27}N_3O_5S$. Calculated (%): C, 52.97; H, 7.06; N, 10.90; S, 8.32. IR, ν/cm^{-1}: 3180—3300 (NH_2), 2248 (CN), 1670 (C=O). ^1H NMR, δ: 9.75 (br.s, 2 H, NH_2); 4.58 (d, 1 H, CHCN, $^3J_{H(2)-H(1)}$ = 11 Hz); 3.79 (m, 4 H, CH_2OCH_2); 3.30 (m, 1 H, H(1)); 2.77 (s, 3 H, NCH_3); 1.50 (s, 6 H, $(CH_3)_2$); 1.42 (m, 2 H, CH_2); 0.70 (t, 3 H, CH_3).

***N*-Methylmorpholinium 5-(1-cyano-3-methyl-1-thiocarbamoylbut-2-yl)-2,2-dimethyl-6-oxo-1,3-dioxacyclohex-4-en-4-olate (4b)** was prepared similarly to compound **4a** using the corresponding aldehyde, isobutanal (**1b**). Yield 3.0 g (75%), m.p. 127—129 °C. Found (%): C, 54.00; H, 7.50; N, 10.30; S, 7.88. $C_{18}H_{29}N_3O_5S$. Calculated (%): C, 54.12; H, 7.32; N, 10.52; S, 8.03. IR, ν/cm^{-1}: 3150, 3300 (NH_2); 2250 (CN); 1652 (C=O). ^1H NMR, δ: 9.78 (br.s, 2 H, NH_2); 5.05 (d, 1 H, CHCN, $^3J_{H(2)-H(1)}$ = 12 Hz); 3.78 (m, 4 H, CH_2OCH_2); 3.47 (dd, 1 H, H(1)); 3.11 (m, 4 H, CH_2NCH_2); 2.75 (s, 3 H, NCH_3); 1.51 (s, 6 H, $(CH_3)_2$); 1.15 (m, 1 H, $\underline{CH}(CH_3)_2$); 0.78 (m, 6 H, $CH(\underline{CH_3})_2$).

***N*-Methylmorpholinium 3-cyano-4-ethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (5). Method *A*.** A suspension of adduct **4a** (10 mmol) and *N*-methylmorpholine (2 mmol) in 15 mL of ethanol was refluxed for 3 h and allowed to stand for 12 h at 0 °C. The resulting precipitate was filtered off and washed with acetone. Yield 2.1 g (73%), m.p. 108—110 °C. Found (%): C, 55.00; H, 7.60; N, 14.72; S, 11.19. $C_{13}H_{21}N_3O_5S$. Calculated (%): C, 55.10; H, 7.47; N, 14.83; S, 11.31. IR, ν/cm^{-1}: 3200 (NH); 2172 (CN); 1678 (CONH). ^1H NMR, δ: 8.46 (br.s, 1 H, NH); 3.77 (m, 4 H, CH_2OCH_2); 3.20 (m, 4 H, CH_2NCH_2); 2.80 (s, 3 H, NCH_3); 2.30 (m, 2 H, $CH_2(3)$); 1.33 (m, 3 H, H(4) and CH_2); 0.84 (t, 3 H, CH_3).

Method *B*. A suspension of propionic aldehyde (**1a**) (10 mmol), cyanothioacetamide (**2**) (10 mmol), Meldrum's acid (**3**) (10 mmol), and *N*-methylmorpholine (12 mmol) in 15 mL of ethanol was refluxed for 3 h and allowed to stand for 12 h at 0 °C. The precipitate was filtered off and washed with acetone. The yield of salt **5** was 1.7 g (61%) and its melting point and TLC characteristics were identical to those of the sample obtained by method *A*.

5-Cyano-4-ethyl-6-mercapto-3,4-dihydropyridin-2(1*H*)-one (6a). Method *C*. A suspension of salt **5** (10 mmol) in 15 mL of ethanol was diluted by a 10% aqueous solution of HCl to pH 5, and the mixture was filtered. After 12 h, the precipitate was filtered off and washed with ethanol. Yield 1.15 g (63%), m.p. 130—132 °C (ethanol). Found (%): C, 52.64; H, 5.38; N,

Table 1. Spectral characteristics of compounds **10a—e**, **11a—e**, and **12e—h**

Compound	IR, ν/cm^{-1}				^{1}H NMR, δ			
	NH	C≡N	NHCO, C=O	NH	H(3)	R, CH_3(4)	SCH_2, NH_2	H(4), Z
10a	3224	2212	1677	10.33	2.70 m	1.06 d	2.45 s	2.25 (m, 1 H, H(4))
10b	3210	2192	1685	10.36	2.20—2.75 m	1.44 m*; 0.88 t	2.46 s	1.44 (m, 1 H, H(4))*
10c	3185	2220	1710	10.38	2.20—2.75 m	1.44 m*; 0.89 t	2.99 q	1.19 (t, 3 H, CH_3); 1.44 (m, 1 H, H(4))*
10d	3190	2200	1682, 1724	10.45	2.25 dd; 2.70 dd ^3J = 18 Hz	1.45 m*; 0.88 t	3.92 s	4.09 (q, 2 H, OCH_2); 1.19 (t, 3 H, CH_3CH_2O); 1.45 (m, 1 H, H(4))*
10e	3250	2203	1660, 1710	10.43	2.10—2.95 m*	3.51 m	4.80 s	2.08 и 7.87 (both d, 2 H, C_6H_4); 7.35—7.70 (m, 5 H, Ph); 2.25 (m, 1 H, H(4))*
11a	3200	2220	1690	12.05	6.42 s	2.33 s	4.23 s	7.33 (s, 5 H, C_6H_5); 5.15 (s, 2 H, OCH_2)
11b	3222	2224	1690	11.96	6.41 s	2.33 s	4.15 s	3.66 (s, 3 H, OCH_3)
11c	3211	2220	1682	12.06	6.40 s	2.30 s	4.49 s	5.20—5.55 (m, 5 H, Ph)
11d	3209	2222	1675	11.99	6.41 s	2.33 s	4.15 s	10.30 (s, 1 H, NHCO); 5.52 (s, 4 H, C_6H_4)
11e	3275	2218	1695	11.87	6.38 s	2.33 s	4.49 s	7.35—8.20 (m, 4 H, C_6H_4)
12e	3385, 3464	—	1650	12.33	6.18 s	2.57 s	7.97 br.s	7.55 (m, 4 H, C_6H_4)
12f	3240, 3415	—	1680, 1700	12.66 br.s	6.21 s	2.57 s	8.40 br.s	7.60—8.15 (m, 4 H, C_6H_4)
12g	3270, 3485	—	1665	12.25 br.s	6.18 s	2.57 s	7.99 br.s	5.50—7.82 (m, 3 H, C_6H_3)
12h	3200—3390	—	1666, 1720	11.89 br.s	6.31 s	2.19 s	8.15 s	8.41 (d, 1 H); 7.30—7.85 (m, 4 H)

* The signals overlap.

Table 2. Yields, melting points, and data of elemental analysis for compounds **10a—e**, **11a—e**, and **12e—h**

Compound	Yield (%) (method)	M.p./°C (solvent for crystallization)	Found / Calculated (%)				Molecular formula
			C	H	N	S	
10a	66 (*E*)	149—151 (ethanol)	52.63 / 52.72	5.38 / 5.53	15.45 / 15.37	17.68 / 17.59	$C_8H_{10}N_2OS$
10b	77 (*E*) 63 (*F*)	176—178 (ethanol)	54.90 / 55.08	6.12 / 6.11	14.06 / 14.27	16.52 / 16.34	$C_9H_{12}N_2OS$
10c	64 (*E*) 71 (*F*)	136—138 (1 : 1 aqueous ethanol)	56.95 / 57.11	6.60 / 6.71	13.10 / 13.32	15.37 / 15.25	$C_{10}H_{14}N_2OS$
10d	68 (*E*) 78 (*F*)	83—85 (1 : 1 aqueous ethanol)	53.84 / 53.71	5.87 / 6.01	10.50 / 10.44	12.12 / 11.95	$C_{12}H_{16}N_2O_3S$
10e	77	153—155 (ethanol)	69.42 / 69.59	4.88 / 5.01	7.55 / 7.73	9.00 / 8.85	$C_{21}H_{18}N_2O_2S$
11a	77	109—111 (AcOH)	61.02 / 61.13	4.55 / 4.49	8.87 / 8.91	10.04 / 10.20	$C_{16}H_{14}N_2O_3S$
11b	81	150—152 (2-propanol)	50.50 / 50.41	4.30 / 4.23	11.59 / 11.76	13.26 / 13.46	$C_{10}H_{10}N_2O_3S$
11c	72	171—173 (AcOH)	65.47 / 65.60	4.60 / 4.72	11.07 / 10.93	12.35 / 12.51	$C_{14}H_{12}N_2OS$
11d	88	199—201 (AcOH)	47.72 / 47.63	3.11 / 3.20	11.02 / 11.11	8.25 / 8.48	$C_{15}H_{12}BrN_3O_2S$
11e	75	307—309 (AcOH)	49.48 / 49.60	2.84 / 3.05	7.80 / 7.71	8.92 / 8.83	$C_{15}H_{11}BrN_2O_2S$
12e	69	293—295 (AcOH)	49.51 / 49.60	2.93 / 3.05	7.82 / 7.71	8.69 / 8.83	$C_{15}H_{11}BrN_2O_2S$
12f	71	300 (decomp.) (AcOH)	54.60 / 54.71	3.22 / 3.37	12.85 / 12.76	9.57 / 9.74	$C_{15}H_{11}N_3O_4S$
12g	68	333—335 (AcOH)	50.86 / 51.01	2.71 / 2.85	7.77 / 7.93	8.88 / 9.08	$C_{15}H_{10}Cl_2N_2O_2S$
12h	80	340 (decomp.) (AcOH)	61.21 / 61.36	3.25 / 3.43	8.14 / 7.95	8.95 / 9.10	$C_{18}H_{12}N_2O_4S$

15.42; S, 17.41. $C_8H_{10}N_2OS$. Calculated (%): C, 52.72; H, 5.53; N, 15.37; S, 17.59. IR, ν/cm^{-1}: 3210 (NH); 2255 (CN); 1700 (CONH). ^{1}H NMR, δ: 12.74 (br.s, 1 H, NH); 4.50 (d, 1 H, H(5), $^3J_{H(5)-H(4)}$ = 10 Hz); 3.57 (br.s, 1 H, SH); 2.50 (m, 2 H, CH_2(3)); 1.43 (m, 3 H, H(4) and CH_2); 0.90 (t, 3 H, CH_3).

Method *D*. A suspension of aldehyde **1a** (10 mmol), cyanothioacetamide (**2**) (10 mmol), Meldrum's acid (**3**) (10 mmol), and *N*-methylmorpholine (12 mmol) in 15 mL of ethanol was refluxed for 3 h. The reaction mixture was cooled to 20 °C and diluted with 10% hydrochloric acid to pH 5. After 12 h, the resulting precipitate was separated and washed with ethanol and heptane. The yield of compound **6a** was 1.31 g (72%) and its melting point and TLC mobility were identical to those of the sample prepared by method *C*.

5-Cyano-6-mercapto-4-methyl-3,4-dihydropyridin-2(1*H*)-one (6c) was prepared by method *D* described above for the synthesis of compound **6a** from acetaldehyde (**1c**). Yield 0.94 g (56%), m.p. 134—136 °C (ethanol). Found (%): C, 49.76; H, 5.00; N, 16.48; S, 18.87. $C_7H_8N_2OS$. Calculated (%): C, 49.98; H, 4.79; N, 16.65; S, 19.06. IR, ν/cm^{-1}: 3450 (NH); 2216, 2250 (CN); 1665 (CONH). ^{1}H NMR, δ: 12.71 (br.s, 1 H, NH); 4.43—4.75 (m, 1 H, H(5)); 3.55 (br.s, 1 H, SH); 2.55 (m, 3 H, H(4) and CH_2); 1.40 (br.s, 3 H, CH_3).

5-Cyano-6-mercapto-4-methylpyridin-2(1*H*)-one (7). A suspension of compound **6c** (10 mmol) in 15 mL of DMSO was heated for 9 h on a boiling water bath. After cooling, the reaction mixture was diluted with 10 mL of water; 2 h later, the precipitate was filtered off and washed with water, ethanol, and hexane. The yield of compound **7** was 0.56 g (34%) and its melting point (270—271 °C) was identical to that of pyridinone **7** obtained previously.[7]

5-Cyano-6-Z-methylthio-4-R-3,4-dihydropyridin-2(1*H*)-ones (10a—e). Method *E*. A suspension of salt **5** (10 mmol) and halide **8** (10 mmol) in 15 mL of ethanol was stirred for 3 h at 20 °C and then diluted with 10 mL of water. The precipitate was filtered off and washed with 40% aqueous ethanol and hexane to give compounds **10a—e** (Tables 1 and 2).

Method *F*. A 10% aqueous solution of KOH (5.6 mL, 10 mmol) and halide **8** (10 mmol) were added to a suspension of compound **6** (10 mmol) in 15 mL of ethanol, and the mixture was stirred for 3 h and diluted with 10 mL of water. The resulting precipitate was separated and washed with 40% aqueous ethanol and hexane to give compounds **10a—e** whose melting points and TLC mobility were identical to those of the samples synthesized by method *E* (Tables 1 and 2).

5-Cyano-4-methyl-6-Z-methylthiopyridin-2(1*H*)-ones (11a—e) were prepared similarly to compounds **10** (method *E*) using pyridone **7** (Tables 1 and 2).

3-Amino-4-methyl-2-Z-thieno[2,3-*b*]pyridin-6(7*H*)-ones (12e—h). A 10% aqueous solution of KOH (5.6 mL, 10 mmol) and halide **9** (10 mmol) were added successively to a solution of thiol **7** (10 mmol) in 10 mL of DMF; the mixture was stirred for 30 min, an additional portion of 10% aqueous solution of KOH (5.6 mL, 10 mmol) was added, and the mixture was stirred for 4 h and diluted with 10 mL of water. The resulting precipitate was filtered off and washed with water, ethanol, and hexane to give compounds **12e—h** (Tables 1 and 2).

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