Synthesis and alkylation of *N*-methylmorpholinium 5-cyano-4-(3- and 4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates

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The reactions of 3- or 4-hydroxybenzaldehydes with cyanothioacetamide and Meldrum's acid in the presence of *N*-methylmorpholine afforded *N*-methylmorpholinium 5-cyano-4-(3- or 4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates, respectively. The resulting compounds were used in the synthesis of substituted 6-alkylthio-1,2,3,4-tetrahydropyridin-2-ones.

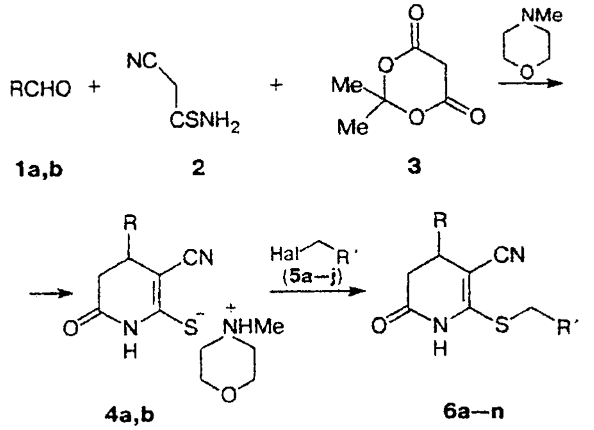
Key words: hydroxybenzaldehydes, cyanothioacetamide, Meldrum's acid, tetrahydropyridinethiolates, alkylation.

Previously, we have studied the reactions of arylmethylidenecyanothioacetamides with Meldrum's acid[1] and condensation of aromatic aldehydes, cyanoacetamide, and Meldrum's acid[2] in the presence of *N*-methylmorpholine. It was found that these reactions proceeded regioselectively to form *N*-methylmorpholinium 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates. The structures of the latter have been established[1] by X-ray diffraction analysis. The results obtained and the data[3] on biological activity of substituted 3-cyanopyridin-2(1*H*)-ones and their hydrogenated analogs stimulated us to develop convenient procedures for the preparation of previously unknown tetrahydropyridones containing a phenolic fragment.

Thus boiling of a mixture of aldehydes (**1a,b**), cyanothioacetamide (**2**), Meldrum's acid (**3**), and *N*-methylmorpholine in ethanol afforded substituted 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates (**4a,b**), which reacted with halides (**5a—j**) to form the corresponding 6-(R'-methylthio)-1,2,3,4-tetrahydropyridin-2-ones (**6a—n**) (Scheme 1).

The structures of tetrahydropyridines **4** and **6** were confirmed by physicochemical and spectral data. Thus their IR spectra have absorption bands of stretching vibrations of the conjugated nitrile group and of the NH group in the regions of 2163—2210 and 3150—3495 cm^{-1}, respectively. The ^{1}H NMR spectra have characteristic signals for the protons of the aromatic substituent, the *N*-methylmorpholinium cation (in **4**), and the alkylthio group (in **6**). The signals for the protons of the tetrahydropyridine nucleus are observed as two doublets of doublets at δ 2.28—2.57 (C(3)H$_{eq}$, ^3J = 5.5—6.5 Hz)

Scheme 1



1, **4**: R = 4-HOC$_6$H$_4$ (**a**), 3-HOC$_6$H$_4$ (**b**)

	Hal	R'		Hal	R'
5a	I	Me	**5f**	Cl	CONHPh
5b	I	H	**5g**	Cl	4-BrC$_6$H$_4$NHCO
5c	Br	Et	**5h**	Cl	CONH$_2$
5d	Cl	Ph	**5i**	Cl	COOEt
5e	Cl	COOMe	**5j**	Br	CH=CH$_2$

	R	R'		R	R'
6a	4-HOC$_6$H$_4$	Me	**6h**	4-HOC$_6$H$_4$	CONH$_2$
6b	4-HOC$_6$H$_4$	H	**6i**	4-HOC$_6$H$_4$	COOEt
6c	4-HOC$_6$H$_4$	Et	**6j**	3-HOC$_6$H$_4$	H
6d	4-HOC$_6$H$_4$	Ph	**6k**	3-HOC$_6$H$_4$	CH=CH$_2$
6e	4-HOC$_6$H$_4$	COOMe	**6l**	3-HOC$_6$H$_4$	Ph
6f	4-HOC$_6$H$_4$	CONHPh	**6m**	3-HOC$_6$H$_4$	COOMe
6g	4-HOC$_6$H$_4$	4-BrC$_6$H$_4$NHCO	**6n**	3-HOC$_6$H$_4$	CONH$_2$

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Table 1. Physicochemical characteristics of 5-cyano-4-R-6-(R′-methylthio)-1,2,3,4-tetrahydropyridin-2-ones (**6a—n**)

Compound	R	R'	Yield (%)	M.p. /°C	Found/Calculated (%) C	H	N	S	Molecular formula
6a	4-HOC_6H_4	Me	84	205—207	61.42 61.29	5.28 5.14	10.07 10.21	11.54 11.69	$C_{14}H_{14}N_2O_2S$
6b	4-HOC_6H_4	H	93	248—250	59.79 59.98	4.82 4.65	10.59 10.76	12.54 12.32	$C_{13}H_{12}N_2O_2S$
6c	4-HOC_6H_4	Et	71	152—154	62.18 62.48	5.74 5.59	9.50 9.71	11.30 11.12	$C_{15}H_{16}N_2O_2S$
6d	4-HOC_6H_4	Ph	68	206—208	67.57 67.84	5.01 4.79	8.57 8.33	9.65 9.53	$C_{19}H_{16}N_2O_2S$
6e	4-HOC_6H_4	COOMe	89	99—101	56.83 56.59	4.70 4.43	9.05 8.80	10.19 10.07	$C_{15}H_{14}N_2O_4S$
6f	4-HOC_6H_4	CONHPh	93	199—201	63.56 63.31	4.70 4.52	11.23 11.07	8.61 8.45	$C_{20}H_{17}N_3O_3S$
6g	4-HOC_6H_4	4-BrC_6H_4NHCO	91	265—266	52.67 52.41	3.21 3.52	9.31 9.17	7.13 7.00	$C_{20}H_{16}BrN_3O_3S$
6h	4-HOC_6H_4	$CONH_2$	66	236—237	55.61 55.43	4.12 4.32	14.05 13.85	10.71 10.57	$C_{14}H_{13}N_3O_3S$
6i	4-HOC_6H_4	COOEt	72	162—164	57.58 57.82	4.99 4.85	8.64 8.43	9.78 9.65	$C_{16}H_{16}N_2O_4S$
6j	3-HOC_6H_4	H	85	223—224	59.72 59.98	4.82 4.65	10.51 10.76	12.57 12.32	$C_{13}H_{12}N_2O_2S$
6k	3-HOC_6H_4	$CH=CH_2$	77	139—141	63.16 62.92	4.71 4.93	9.94 9.78	11.57 11.20	$C_{15}H_{14}N_2O_2S$
6l	3-HOC_6H_4	Ph	67	153—156	67.57 67.84	4.71 4.79	8.64 8.33	9.73 9.53	$C_{19}H_{16}N_2O_2S$
6m	3-HOC_6H_4	COOMe	79	136—138	56.84 56.59	4.76 4.43	8.54 8.80	10.22 10.07	$C_{15}H_{14}N_2O_4S$
6n	3-HOC_6H_4	$CONH_2$	69	205—207	55.74 55.43	4.51 4.32	13.97 13.85	10.85 10.57	$C_{14}H_{13}N_3O_3S$

and 2.63—2.93 (C(3)H_{ax}, ^3J = 6.8—7.7 Hz), a doublet of doublets (for **4**) or sometimes a triplet (for **6**) at δ 3.51—3.87 (C(4)H), and a singlet at δ 8.53—9.27 (NH). The close values of the vicinal spin-spin coupling constants of the protons of the C(3)H_2 group are indicative of the equatorial position of the proton at the C(4) atom, which we have also noted in the instances studied previously.[1]

Experimental

The ^{1}H NMR spectra were recorded on Bruker WP-100 SY (100 MHz) (for compounds **4a,b**) and Bruker AC-300 (300 MHz) (for compounds **6a—n**) instruments in DMSO-d_6 with Me_4Si as the internal standard. The IR spectra were obtained on an IKS-29 spectrophotometer in Nujol mulls. The course of the reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in an acetone—hexane system. Spots were visualized with iodine vapor.

***N*-Methylmorpholinium 5-cyano-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (4a).** A suspension of 4-hydroxybenzaldehyde (**1a**) (1.22 g, 10 mmol), cyanothioacetamide (**2**) (1 g, 10 mmol), Meldrum's acid (**3**) (1.44 g, 10 mmol), and *N*-methylmorpholine (1.5 mL, 15 mmol) in EtOH (30 mL) was refluxed for 3 h and then kept for 12 h. The precipitate that formed was filtered off and washed with acetone. Salt **4a** was obtained in a yield of 2.68 g (77%), m.p. 153—155 °C. Found (%): C, 58.99; H, 5.81; N, 12.24; S, 9.51. $C_{17}H_{21}N_3O_3S$. Calculated (%): C, 58.77; H, 6.09; N, 12.09; S, 9.23. IR, ν/cm^{-1}: 3165 (NH); 2163 (C≡N); 1630 (C=O). ^{1}H NMR, δ: 2.28 (dd, 1 H, C(3)H_{eq}, ^2J = 16.9 Hz, ^3J = 4.3 Hz); 2.65 (dd, 1 H, C(3)H_{ax}, ^3J = 6.5 Hz); 2.78 (s, 3 H, MeN); 3.16 (t, 4 H, CH_2NCH_2, ^3J = 4.8 Hz); 3.52 (dd, 1 H, C(4)H); 3.76 (t, 4 H, CH_2OCH_2, ^3J = 4.8 Hz); 6.65 and 6.96 (both d, 4 H, H—Ar, ^3J = 8.6 Hz); 8.53 (br.s, 1 H, NH); 9.18 (br.s, 1 H, OH).

***N*-Methylmorpholinium 5-cyano-4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (4b)** was prepared analogously from 3-hydroxybenzaldehyde (**1b**). The yield was 2.33 g (67%), m.p. 165—167 °C. Found (%): C, 58.52; H, 6.28; N, 11.81; S, 9.03. $C_{17}H_{21}N_3O_3S$. Calculated (%): C, 58.77; H, 6.09; N, 12.09; S, 9.23. IR, ν/cm^{-1}: 3180 (NH); 2168 (C≡N); 1605, 1680 (C=O). ^{1}H NMR, δ: 2.27 (dd, 1 H, C(3)H_{eq}, ^2J = 16.0 Hz, ^3J = 4.0 Hz); 2.75 (dd, 1 H, C(3)H_{ax}, ^3J = 8.3 Hz); 2.79 (s, 3 H, MeN); 3.17 (t, 4 H, CH_2NCH_2, ^3J = 4.9 Hz); 3.51 (dd, 1 H, C(4)H); 3.77 (t, 4 H, CH_2OCH_2, ^3J = 4.9 Hz); 6.61 (m, 3 H, H—Ar); 7.07 (t, 1 H, H—Ar, ^3J = 7.5 Hz); 8.54 (br.s, 1 H, NH); 9.30 (br.s, 1 H, OH).

Table 2. IR and ^{1}H NMR spectra of substituted 5-cyano-4-R-6-(R′-methylthio)-1,2,3,4-tetrahydropyridin-2-ones (**6a—n**)

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz)
6a	3365 (NH); 2197 (C≡N); 1610, 1682 (C=O)	1.28 (t, 3 H, Me, $^3J = 6.5$); 2.56 (dd, 1 H, C(3)H_{eq}, $^2J = 16.9$, $^3J = 6.5$); 2.89 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.05 (m, 2 H, CH_2S); 3.80 (pseudotriplet, 1 H, C(4)H); 6.70 and 6.96 (both d, 4 H, H—Ar, $^3J = 8.7$); 9.18 (s, 1 H, NH); 10.41 (s, 1 H, OH)
6b	3330 (NH); 2200 (C≡N); 1600, 1680 (C=O)	2.52 (s, 3 H, MeS); 2.56 (dd, 1 H, C(3)H_{eq}, $^2J = 17.0$, $^3J = 6.5$); 2.87 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.79 (pseudotriplet, 1 H, C(4)H); 6.70 and 6.97 (both d, 4 H, H—Ar, $^3J = 8.7$); 9.14 (s, 1 H, NH); 10.34 (s, 1 H, OH)
6c	3345 (NH); 2202 (C≡N); 1605, 1685 (C=O)	1.05 (t, 3 H, Me, $^3J = 6.6$); 1.64 (m, 2 H, $C\underline{H}_2CH_2S$); 2.56 (dd, 1 H, C(3)H_{eq}, $^2J = 16.9$, $^3J = 6.3$); 2.90—3.10 (m, 3 H, C(3)H_{ax} and CH_2S); 3.79 (pseudotriplet, 1 H, C(4)H); 6.70 and 6.95 (both d, 4 H, H—Ar, $^3J = 8.7$); 9.17 (s, 1 H, NH); 10.39 (s, 1 H, OH)
6d	3170, 3360 (NH); 2208 (C≡N); 1600, 1690 (C=O)	2.35 (dd, 1 H, C(3)H_{eq}, $^2J = 17.0$, $^3J = 6.1$); 2.63 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.70 (dd, 1 H, C(4)H); 4.24 and 4.32 (both d, 2 H, CH_2S, $^2J = 18.5$); 6.64 and 6.77 (both d, 4 H, H—Ar, $^3J = 8.7$); 7.30 (m, 5 H, Ph); 9.14 (s, 1 H, NH); 10.54 (s, 1 H, OH)
6e	3210—3360 (NH); 2196 (C≡N); 1680 (2 C=O)	2.55 (dd, 1 H, C(3)H_{eq}, $^2J = 17.0$, $^3J = 6.0$); 2.85 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.69 (s, 3 H, MeO); 3.84 (dd, 1 H, C(4)H); 3.93 (s, 2 H, CH_2S); 6.72 and 6.98 (both d, 4 H, H—Ar, $^3J = 8.7$); 9.18 (s, 1 H, NH); 10.43 (s, 1 H, OH)
6f	3350, 3450 (2 NH); 2200 (C≡N); 1620, 1680, 1725 (2 C=O)	2.57 (dd, 1 H, C(3)H_{eq}, $^2J = 16.7$, $^3J = 5.6$); 2.88 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.86 (dd, 1 H, C(4)H); 3.92 (s, 2 H, CH_2S); 6.70 and 6.96 (both d, 4 H, H—Ar, $^3J = 8.7$); 7.08—7.57 (m, 5 H, H—Ph); 9.18 (s, 1 H, NH); 10.30 (s, 1 H, NHCO); 10.68 (s, 1 H, OH)
6g	3150—3330 (2 NH); 2207 (C≡N); 1605, 1660, 1690 (2 C=O)	2.56 (dd, 1 H, C(3)H_{eq}, $^2J = 16.5$, $^3J = 5.8$); 2.86 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.84 (dd, 1 H, C(4)H); 3.93 (s, 2 H, CH_2S); 6.70 and 6.98 (both d, 4 H, H—Ar, $^3J = 8.7$); 7.43 and 7.55 (both d, 4 H, 4-BrC_6H_4, $^3J = 8.7$); 9.19 (s, 1 H, NH); 10.40 (s, 1 H, NHCO); 10.61 (s, 1 H, OH)
6h	3180, 3360, 3465 (NH, NH_2); 2210 (C≡N); 1610, 1665, 1695 (2 C=O)	2.55 (dd, 1 H, C(3)H_{eq}, $^2J = 15.7$, $^3J = 5.6$); 2.86 (dd, 1 H, C(3)H_{ax}, $^3J = 7.2$); 3.63 and 3.74 (both d, 2 H, CH_2S, $^2J = 16.8$); 3.83 (dd, 1 H, C(4)H); 6.70 and 6.98 (both d, 4 H, H—Ar, $^3J = 8.7$); 7.49 and 7.83 (both s, 2 H, $CONH_2$); 9.18 (s, 1 H, NH); 11.04 (s, 1 H, OH)
6i	3180, 3360 (NH); 2190 sh., 2207 (C≡N); 1605, 1695 (2 C=O)	1.26 (t, 3 H, Me, $^3J = 6.8$); 2.54 (dd, 1 H, C(3)H_{eq}, $^2J = 16.9$, $^3J = 6.3$); 2.82 (dd, 1 H, C(3)H_{ax}, $^3J = 7.3$); 3.82 (dd, 1 H, C(4)H); 3.85 and 3.88 (both d, 2 H, CH_2S, $^2J = 17.1$); 4.15 (q, 2 H, CH_2O, $^3J = 6.8$); 6.71 and 6.98 (both d, 4 H, H—Ar, $^3J = 8.7$); 9.18 (s, 1 H, NH); 10.47 (s, 1 H, OH)
6j	3165, 3330 (NH); 2195 (C≡N); 1680 (C=O)	2.54 (s, 3 H, MeS); 2.57 (dd, 1 H, C(3)H_{eq}, $^2J = 17.4$, $^3J = 5.5$); 2.93 (dd, 1 H, C(3)H_{ax}, $^3J = 7.7$); 3.83 (dd, 1 H, C(4)H); 6.60 (m, 3 H, H—Ar); 7.12 (t, 1 H, H—Ar, $^3J = 7.6$); 9.24 (s, 1 H, NH); 10.39 (s, 1 H, OH)
6k	3180, 3345 (NH); 2200 (C≡N); 1685 (C=O)	2.55 (dd, 1 H, C(3)H_{eq}, $^3J = 5.4$*); 2.86 (dd, 1 H, C(3)H_{ax}, $^2J = 17.6$, $^3J = 7.3$); 3.60—3.87 (m, 2 H, CH_2S); 4.83 (dd, 1 H, C(4)H, $^3J = 5.4$, $^3J = 7.3$); 5.14 (d, 1 H, CH_2=, $^3J = 14.2$); 5.19 (d, 1 H, CH_2=, $^3J = 6.8$); 5.86 (m, 1 H, CH=); 6.63 (m, 3 H, H—Ar); 7.12 (t, 1 H, H—Ar, $^3J = 7.2$); 9.24 (s, 1 H, NH); 10.47 (s, 1 H, OH)
6l	3190, 3350 (NH); 2205 (C≡N); 1675 (C=O)	2.42 (dd, 1 H, C(3)H_{eq}, $^2J = 16.5$, $^3J = 5.1$); 2.65 (dd, 1 H, C(3)H_{ax}, $^3J = 7.7$); 3.72 (dd, 1 H, C(4)H); 4.29 (s, 2 H, CH_2S); 6.43 and 6.63 (both d, 2 H, H—Ar, $^3J = 8.5$); 6.53 (s, 1 H, H—Ar); 7.08 (t, 1 H, H—Ar, $^3J = 7.3$); 7.31 (m, 5 H, Ph); 9.23 (s, 1 H, NH); 10.57 (s, 1 H, OH)
6m	3180, 3390 (NH); 2198 (C≡N); 1690, 1740 (2 C=O)	2.57 (dd, 1 H, C(3)H_{eq}, $^2J = 17.4$, $^3J = 5.1$); 2.88 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.70 (s, 3 H, MeO); 3.87 (dd, 1 H, C(4)H); 3.91 and 3.99 (both d, 2 H, CH_2S, $^2J = 19.8$); 6.63 (m, 3 H, H—Ar); 7.12 (t, 1 H, H—Ar, $^3J = 7.3$); 9.27 (s, 1 H, NH); 10.50 (s, 1 H, OH)
6n	3225, 3330, 3495 (NH, NH_2); 2208 (C≡N); 1600, 1630, 1670, 1710 (2 C=O)	2.57 (dd, 1 H, C(3)H_{eq}, $^2J = 16.2$, $^3J = 5.3$); 2.90 (dd, 1 H, C(3)H_{ax}, $^3J = 6.8$); 3.65 and 3.74 (both d, 2 H, CH_2S, $^2J = 17.1$); 3.84 (dd, 1 H, C(4)H); 6.62 (m, 3 H, H—Ar); 7.10 (t, 1 H, H—Ar, $^3J = 7.1$); 7.47 and 7.82 (both s, 2 H, $CONH_2$); 9.25 (s, 1 H, NH); 11.09 (s, 1 H, OH)

* The signal of C(3)H partially overlaps with the signal of DMSO.

5-Cyano-4-R-6-(R′-methylthio)-1,2,3,4-tetrahydropyridin-2-ones (6a—n) (general procedure). A suspension of the corresponding salt **4** (10 mmol) and halide 5 (10 mmol) in 80% EtOH (30 mL) was heated to boiling and filtered. After 12 h, the precipitate that formed was separated and washed with ethanol and hexane. 5-Cyano-6-ethylthio-4-(4-hydroxyphenyl)- (**6a**), 5-cyano-4-(4-hydroxyphenyl)-6-methylthio- (**6b**), 5-cyano-4-(4-hydroxyphenyl)-6-propylthio- (**6c**), 6-benzylthio-5-cyano-4-(4-hydroxyphenyl)- (**6d**), 5-cyano-4-(4-hydroxyphenyl)-6-methoxycarbonylmethylthio- (**6e**), 5-cyano-4-(4-hydroxyphenyl)-6-phenylcarbamoylmethylthio- (**6f**), 6-(4-bromophenylcarbamoylmethylthio)-5-cyano-4-(4-hydroxyphenyl- (**6g**), 6-carbamoylmethylthio-5-cyano-4-(4-hydroxyphenyl)- (**6h**), 5-cyano-6-ethoxycarbonylmethylthio-4-(4-hydroxyphenyl)- (**6i**), 5-cyano-4-(3-hydroxyphenyl)-6-methylthio- (**6j**), 6-allylthio-5-cyano-4-(3-hydroxyphenyl)- (**6k**), 6-benzylthio-5-cyano-4-(3-hydroxyphenyl)- (**6l**), 5-cyano-4-(3-hydroxyphenyl)-6-methoxycarbonylmethylthio- (**6m**), and 6-carbamoylmethylthio-5-cyano-4-(3-hydroxyphenyl)-1,2,3,4-tetrahydropyridin-2-one (**6n**) were obtained. Their physicochemical and spectral characteristics are given in Tables 1 and 2, respectively.

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