N-Methylmorpholinium 4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates: synthesis and properties

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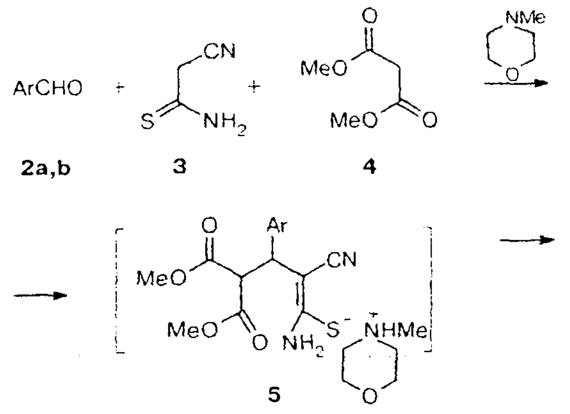
Reactions of aromatic aldehydes with cyanothioacetamide and dimethyl malonate in the presence of *N*-methylmorpholine afforded *N*-methylmorpholinium 4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates. The latter were used to synthesize substituted 6-(alkylthio)-2-oxo-1,2,3,4-tetrahydropyridines.

Key words: aromatic aldehydes, cyanothioacetamide, dimethyl malonate, *N*-methylmorpholine, tetrahydropyridines, Meldrum's acid, alkylation.

At present, there are still few substituted sulfur-containing tetrahydropyridines; in addition, this group of organic compounds is inadequately studied.[1] However, considering their potential biological importance,[2] investigations aimed at developing convenient methods for the synthesis of such heterocycles become topical.

In the present work, a method for the synthesis of *N*-methylmorpholinium 4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates (**1**) is proposed. The method is based on the reaction of aromatic aldehydes **2** with cyanothioacetamide (**3**) and dimethyl malonate (**4**) in the presence of an excess of *N*-methylmorpholine in ethanol (~20 °C). This reaction seems to proceed *via* an intermediate Michael adduct **5**. Alkylation of salts **1** with halides **6** gave the corresponding 6-(alkylthio)-1,2,3,4-tetrahydropyridines **7**.

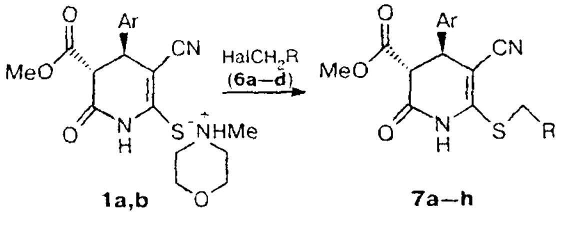


2a,b **3** **4** **5**

1, **2**: Ar = 4-ClC$_6$H$_4$ (**a**), 2-MeOC$_6$H$_4$ (**b**)

Compound	Hal	R
6a	I	H
6b	I	Me
6c	Cl	CONH$_2$
6d	Cl	4-BrC$_6$H$_4$NHCO

In the ^{1}H NMR spectra of compounds **1** and **7** (see Table 1), the H(3) and H(4) protons of the tetrahydropyridine ring appear as doublets at δ 3.56—3.97 and δ 3.97—4.47, respectively ($^3J_{H(3),H(4)}$ = 4.0—8.6 Hz). According to the Carplus—Conroy equation,[3] such spin-spin coupling constants have to correspond to a torsional C(3)H—C(4)H angle of 30—60° or 114—140°. ^{1}H NMR data for isostructural analogs of compounds **1** and **7** [2] suggest that these protons are *trans*-diequatorial, the aryl substituent and the COOMe group being arranged *trans*-diaxially.



1a,b **7a—h**

Compound	Ar	R
7a	4-ClC$_6$H$_4$	H
7b	4-ClC$_6$H$_4$	Me
7c	4-ClC$_6$H$_4$	CONH$_2$
7d	4-ClC$_6$H$_4$	4-BrC$_6$H$_4$NHCO
7e	2-MeOC$_6$H$_4$	H
7f	2-MeOC$_6$H$_4$	Me
7g	2-MeOC$_6$H$_4$	CONH$_2$
7h	2-MeOC$_6$H$_4$	4-BrC$_6$H$_4$NHCO

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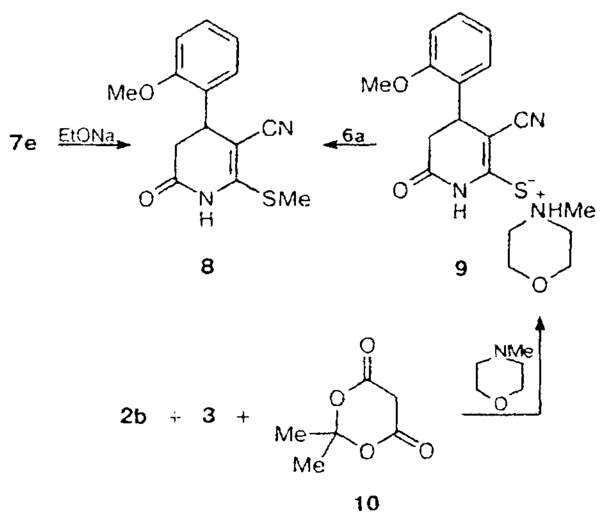

When reacting with sodium ethoxide in ethanol (~50 °C), compound **7e** is transformed into tetrahydropyridine **8**. The latter was also obtained in an independent way from thiolate **9** prepared according to the known procedure[4] by refluxing a mixture of aldehyde **2b**, cyanothioacetamide **3**, and Meldrum's acid **10** in the presence of *N*-methylmorpholine.

Experimental

IR spectra were recorded on an IKS-29 spectrophotometer (Vaseline oil). ^{1}H NMR spectra were recorded on Bruker WP-100 SY (100 MHz) (for compounds **1** and **9**), Bruker WM-250 (250 MHz) (for **7**), and Bruker AC-300 instruments (300 MHz) (for **8**) in DMSO-d$_6$ with Me$_4$Si as the internal standard. The course of the reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates in acetone—hexane (3 : 5).

***N*-Methylmorpholinium 4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates (1).** Cyanothioacetamide (**3**) (2 g, 20 mmol) and, after 5 min, dimethyl malonate (**4**) (2.29 mL, 20 mmol) and *N*-methylmorpholine (2.53 mL, 25 mmol) were added in succession with stirring to a mixture of the corresponding aldehyde **2a,b** (20 mmol) and three drops of *N*-methylmorpholine in 30 mL of EtOH (~20 °C). After the starting compounds were dissolved, the reaction mixture was kept for 12 h. The precipitate that formed was filtered off and washed with acetone. The spectral parameters for compounds **1** are presented in Table 1.

***N*-Methylmorpholinium 4-(4-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (1a).** Yield 5.43 g (64%), m.p. 160—163 °C. Found (%): C, 54.03; H, 5.44; N, 9.73; S, 7.68. $C_{19}H_{22}ClN_3O_4S$. Calculated (%): C, 53.83; H, 5.23; N, 9.91; S, 7.56.

***N*-Methylmorpholinium 5-cyano-3-methoxycarbonyl-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (1b).** Yield 5.96 g (71%), m.p. 154—156 °C. Found (%): C, 57.53; H, 6.28; N, 9.77; S, 7.49. $C_{20}H_{25}N_3O_5S$. Calculated (%): C, 57.26; H, 6.01; N, 10.02; S, 7.64.

6-Alkylthio-4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridines (7). A mixture of the corresponding salt **1** (5 mmol) and halide **6** (5 mmol) in 20 mL of 80% EtOH was heated until the starting compounds were dissolved and then filtered through a paper filter. After 12 h, the precipitate that formed was isolated and washed with EtOH and hexane. The spectral parameters for compounds **7** are presented in Table 1.

4-(4-Chlorophenyl)-5-cyano-3-methoxycarbonyl-6-methylthio-2-oxo-1,2,3,4-tetrahydropyridine (7a). Yield 1.36 g (81%), m.p. 186—188 °C. Found (%): C, 53.77; H, 3.68; N, 8.59; S, 9.36. $C_{15}H_{13}ClN_2O_3S$. Calculated (%): C, 53.49; H, 3.89; N, 8.32; S, 9.52.

4-(4-Chlorophenyl)-5-cyano-6-ethylthio-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine (7b). Yield 1.49 g (85%), m.p. 161—163 °C. Found (%): C, 54.92; H, 4.44; N, 7.69; S, 9.42. $C_{16}H_{15}ClN_2O_3S$. Calculated (%): C, 54.78; H, 4.31; N, 7.98; S, 9.14.

6-Carbamoylmethylthio-4-(4-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine (7c). Yield 1.2 g (63%), m.p. 207—209 °C. Found (%): C, 50.85; H, 3.58; N, 11.21; S, 8.77. $C_{16}H_{14}ClN_3O_4S$. Calculated (%): C, 50.60; H, 3.72; N, 11.06; S, 8.44.

6-(4-Bromophenylcarbamoylmethylthio)-4-(4-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine (7d). Yield 2.49 g (93%), m.p. 239—241 °C. Found (%): C, 49.78; H, 3.53; N, 7.56; S, 6.22. $C_{22}H_{17}BrClN_3O_4S$. Calculated (%): C, 49.41; H, 3.20; N, 7.86; S, 6.00.

5-Cyano-3-methoxycarbonyl-4-(2-methoxyphenyl)-6-methylthio-2-oxo-1,2,3,4-tetrahydropyridine (7e). Yield 1.25 g (75%), m.p. 176—178 °C. Found (%): C, 57.91; H, 4.65; N, 8.49; S, 9.84. $C_{16}H_{16}N_2O_4S$. Calculated (%): C, 57.82; H, 4.85; N, 8.43; S, 9.65.

5-Cyano-6-ethylthio-3-methoxycarbonyl-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine (7f). Yield 1.14 g (66%), m.p. 153—155 °C. Found (%): C, 58.77; H, 5.45; N, 8.41; S, 9.41. $C_{17}H_{18}N_2O_4S$. Calculated (%): C, 58.94; H, 5.24; N, 8.09; S, 9.26.

6-Carbamoylmethylthio-5-cyano-3-methoxycarbonyl-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine (7g). Yield 1.71 g (91%), m.p. 211—213 °C. Found (%): C, 54.72; H, 4.28; N, 11.33; S, 8.66. $C_{17}H_{17}N_3O_5S$. Calculated (%): C, 54.39; H, 4.56; N, 11.19; S, 8.54.

6-(4-Bromophenylcarbamoylmethylthio)-5-cyano-3-methoxycarbonyl-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine (7h). Yield 2.31 g (87%), m.p. 223—225 °C. Found (%): C, 52.33; H, 4.06; N, 7.68; S, 6.39. $C_{23}H_{20}BrN_3O_5S$. Calculated (%): C, 52.08; H, 3.80; N, 7.92; S, 6.05.

5-Cyano-4-(2-methoxyphenyl)-6-methylthio-2-oxo-1,2,3,4-tetrahydropyridine (8). ***A.*** A solution of EtONa prepared from Na metal (0.16 g, 7 mmol) and EtOH (10 mL) was added with stirring to a suspension of compound **7e** (1.66 g, 5 mmol) in 12 mL of EtOH. The reaction mixture was heated to ~50 °C, kept at this temperature for 30 min, and then filtered through a paper filter. After 12 h, the precipitate that formed was isolated and washed with EtOH and hexane.

B. A mixture of salt **9** (1.81 g, 5 mmol) and MeI (**6a**) (0.31 mL, 5 mmol) in 30 mL of EtOH was heated to the boiling point and filtered through a paper filter. After 12 h, the precipitate that formed was isolated and washed with EtOH and hexane. Yield (*A*) 0.86 g (63%), (*B*) 1.25 g (91%), m.p. 191—193 °C. Found (%): C, 61.52; H, 5.34; N, 10.03; S, 11.81. $C_{14}H_{14}N_2O_2S$. Calculated (%): C, 61.29; H, 5.14; N, 10.21; S, 11.69. IR, ν/cm^{-1}: 3200 (NH), 2190 (CN), 1680 (CO). ^{1}H NMR, δ: 2.53 (s, 3 H, SMe); 2.59 (dd, 1 H, H(3),

Table 1. Spectral parameters for compounds **1a,b** and **7a—h**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ, J/Hz
1a	3150 (NH), 2190 (CN), 1690, 1735 (CO)	2.80 (s, 3 H, NMe); 3.18 (t, 4 H, CH_2NCH_2, ^3J = 4.5); 3.56 (m, 4 H, OMe and H(3)); 3.77 (t, 4 H, CH_2OCH_2, ^3J = 4.5); 3.97 (d, 1 H, H(4), ^3J = 8); 7.25 and 7.37 (both d, 4 H, Ar, ^3J = 7.2); 9.12 (br.s, 1 H, NH)
1b	3150 (NH), 2180 (CN), 1680, 1740 (CO)	2.76 (s, 3 H, NMe); 3.14 (t, 4 H, CH_2NCH_2, ^3J = 4.5); 3.41 (d, 1 H, H(3), ^3J = 4); 3.65 (s, 3 H, COOMe); 3.81 (m, 7 H, OMe and CH_2OCH_2); 4.28 (d, 1 H, H(4), ^3J = 4); 7.03—7.26 (m, 4 H, C_6H_4); 9.12 (br.s, 1 H, NH)
7a	3210 (NH), 2190 (CN), 1680, 1755 (CO)	2.57 (s, 3 H, SMe); 3.64 (s, 3 H, OMe); 3.97 (d, 1 H, H(3), ^3J = 8.6); 4.26 (d, 1 H, H(4), ^3J = 8.6); 7.28 and 7.39 (both d, 4 H, Ar, ^3J = 7.3); 10.87 (br.s, 1 H, NH)
7b	3180 (NH), 2203 (CN), 1695, 1750 (CO)	1.29 (t, 3 H, Me, ^3J = 8.2); 3.07 (m, 2 H, SCH_2); 3.68 (s, 3 H, OMe); 3.95 (d, 1 H, H(3), ^3J = 8.5); 4.28 (d, 1 H, H(4), ^3J = 8.5); 7.27 and 7.39 (both d, 4 H, Ar, ^3J = 7.2); 10.88 (br.s, 1 H, NH)
7c	3140—3260 (NH, NH_2), 2204 (CN), 1665, 1740 (CO)	3.63 (s, 3 H, OMe); 3.68 and 3.78 (both d, 2 H, SCH_2, ^2J = 14.5); 3.92 (d, 1 H, H(3), ^3J = 7.2); 4.27 (d, 1 H, H(4), ^3J = 7.2); 7.28 and 7.39 (both d, 4 H, Ar, ^3J = 7.2); 7.51 and 7.84 (both br.s, 2 H, NH_2); 11.54 (br.s, 1 H, NH)
7d	3210—3310 (NH), 2205 (CN), 1680, 1730, 1755 (CO)	3.64 (s, 3 H, OMe); 3.87 (d, 1 H, H(3), ^3J = 7.7); 3.94 (br.s, 2 H, SCH_2); 4.29 (d, 1 H, H(4), ^3J = 7.7); 7.24 and 7.36 (both d, 4 H, 4-ClC_6H_4, ^3J = 7.2); 7.45 and 7.58 (both d, 4 H, 4-BrC_6H_4, ^3J = 7.6); 10.41 (br.s, 1 H, CONH); 11.08 (br.s, 1 H, NH)
7e	3240 (NH), 2200 (CN), 1675, 1750 (CO)	2.53 (s, 3 H, SMe); 3.72 (s, 3 H, COOMe); 3.80 (d, 1 H, H(3), ^3J = 5.9); 3.88 (s, 3 H, OMe); 4.43 (d, 1 H, H(4), ^3J = 5.9); 6.93 (t, ^3J = 6.8), 7.04 (br.d, ^3J = 7.5), and 7.30 (t, ^3J = 6.8) (4 H, C_6H_4); 10.75 (br.s, 1 H, NH)
7f	3210 (NH), 2204 (CN), 1695, 1750 (CO)	1.32 (t, 3 H, Me, ^3J = 7.8); 3.06 (m, 2 H, SCH_2); 3.70 (s, 3 H, COOMe); 3.78 (d, 1 H, H(3), ^3J = 5.9); 3.87 (s, 3 H, OMe); 4.44 (d, 1 H, H(4), ^3J = 5.9); 6.94 (t, ^3J = 7.1), 7.04 (d, ^3J = 8.2), and 7.32 (t, ^3J = 7.1) (4 H, C_6H_4); 10.75 (br.s, 1 H, NH)
7g	3210, 3420 (NH, NH_2), 2195 (CN), 1680, 1730 (CO)	3.68 (br.s, 5 H, COOMe and SCH_2); 3.80 (d, 1 H, H(3), ^3J = 6.4); 4.87 (s, 3 H, OMe); 4.45 (d, 1 H, H(4), ^3J = 6.4); 6.93 (t, ^3J = 7.3), 7.02 and 7.08 (both d, ^3J = 7.7), and 7.31 (t, ^3J = 7.3) (4 H, C_6H_4); 7.57 and 7.79 (both br.s, 2 H, NH_2); 11.34 (br.s, 1 H, NH)
7h	3270, 3420 (NH), 2205 (CN), 1695, 1760 (CO)	3.68 (s, 3 H, COOMe); 3.78 (d, 1 H, H(3), ^3J = 7.3); 3.85 (s, 3H, OMe); 3.94 (s, 2 H, SCH_2); 4.47 (d, 1 H, H(4), ^3J = 7.3); 6.92 (t, ^3J = 7.1), 7.02 and 7.07 (both d, ^3J = 7.6), and 7.31 (t, ^3J = 7.1) (4 H, C_6H_4); 7.44 and 7.56 (both d, 4 H, 4-BrC_6H_4, ^3J = 7.6); 10.35 (br.s, 1 H, CONH); 10.92 (br.s, 1 H, NH)

^2J = 17.2 Hz, ^3J = 4.8 Hz); 2.87 (dd, 1 H, H(3), ^2J = 17.2 Hz, ^3J = 8.1 Hz); 3.83 (s, 3 H, OMe); 4.24 (t, 1 H, H(4), ^3J = 6.3 Hz); 6.91 (^3J = 7.1 Hz), 7.02 (^3J = 6.9 Hz), 7.25 (^3J = 7.1 Hz) (all t, 4 H, C_6H_4); 10.34 (br.s, 1 H, NH).

***N*-Methylmorpholinium 5-cyano-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate (9)** was obtained according to the known procedure.[4] Yield 2.82 g (78%), m.p. 148—150 °C. Found (%): C, 60.07; H, 6.57; N, 11.68; S, 8.91. $C_{18}H_{23}N_3O_3S$. Calculated (%): C, 59.81; H, 6.41; N, 11.62; S, 8.87. IR, ν/cm^{-1}: 3248 (NH), 2200 (CN), 1680 (CO). ^{1}H NMR, δ: 2.27 (dd, 1 H, H(3), ^2J = 15.5 Hz, ^3J = 3.9 Hz); 2.65 (dd, 1 H, H(3), ^2J = 15.5 Hz, ^3J = 7.8 Hz); 2.80 (s, 3 H, NMe); 3.19 (t, 4 H, CH_2NCH_2, ^3J = 4.7 Hz); 3.80 (m, 5 H, H(4) and CH_2OCH_2); 6.80—7.32 (m, 4 H, C_6H_4); 8.54 (br.s, 1 H, NH).

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