SYNTHESIS OF SOME 5,6-DIHYDRO-7H-1,4,2-OXATHIAZEPIN-7-ONES AND 5H-4,1,3-BENZOXATHIAZEPIN-5-ONES

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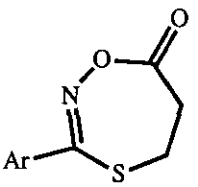
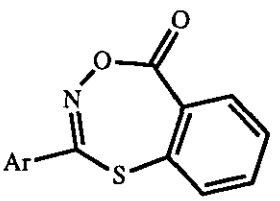
Abstract - The novel heterocyclic systems 5,6-dihydro-7H-1,4,2-oxathiazepin-7-one (**1**) and 5H-4,1,3-benzoxathiazepin-5-one (**2**) were prepared by the reaction of hydroximoyl chlorides (**3**) with mercapto-carboxylic acids, followed by cyclization with 1,3-dicyclohexylcarbodiimide (**6**) or 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide HCl (**7**).

As part of our investigation of novel heterocyclic systems, it was of interest to synthesize the previously unreported 5,6-dihydro-7H-1,4,2-oxathiazepin-7-one ring system (**1**) and its benzo-fused analogue (**2**).



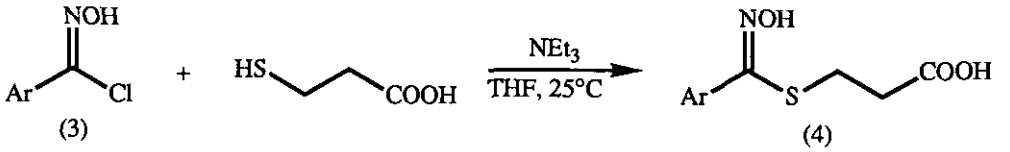
(1)



(2)

The synthetic approach adopted for **1** involved the reaction of an arylhydroximoyl chloride (**3**)[1] with 3-mercaptopropionic acid (via in situ formation of the nitrile oxide with triethylamine) to give the corresponding oxime acid (**4**), followed by cyclization with a diimide to give **1** (cf. Masaki et al.[2]). Similarly the use of thiosalicylic acid instead of 3-mercaptopropionic acid was expected to afford the benzoxathiazepinone system (**2**) after diimide cyclization. Although reactions of hydroximoyl chlorides with sulfur nucleophiles are well known,[3,4] there are few reports of reactions with mercapto-carboxylic acids in the literature.[4]

Thus the hydroximoyl chloride (**3**) and 3-mercaptopropionic acid (1 mol eq.) were dissolved in dry tetrahydrofuran and a solution of triethylamine (1 mol eq.) in tetrahydrofuran added slowly at room temperature. After stirring overnight the reaction was worked up and the crude oxime acid (**4a-d**) isolated by bicarbonate extraction and used without further purification. The oxime acids (**4a-d**) showed two triplets in the ^{1}H nmr spectra[5] for the methylenes (J = 8 Hz) as well as a broad exchangeable singlet for the oxime and acid protons between δ 9-11. The infrared spectra[5] of the oxime acids (**4a-d**) showed broad, strong bands around 3300 and 2550 cm^{-1} due to the hydroxyl group(s) and also exhibited a carbonyl stretch in the range of 1695-1715 cm^{-1}. The oxime acid (**4a-d**) was then treated with either 1,3-dicyclohexylcarbodiimide (DCC) (**6**) (1 mol eq.) in tetrahydrofuran or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (**7**) (1 mol eq.) in methylene chloride (see Table 1) at room temperature and stirred overnight. Work up of the reaction followed by either radial chromatography (chloroform elution) or trituration of the crude product with ether gave the 3-substituted 5,6-dihydro-7H-1,4,2-oxathiazepin-7-one (**1a-d**) as a colourless solid (Table 1). The ^{1}H nmr spectra[6] for (**1a-d**) showed two triplets (J = 7 Hz) for the methylenes and no exchangeable protons, consistent with ring closure, as was the increase in the frequency of the carbonyl stretch in the infrared spectra[6] to 1765-1770 cm^{-1}. The ^{13}C nmr and mass spectra were also consistent with ring closure having occurred.[6]



(1) and (4)	Ar
a	2-thienyl
b	Ph
c	3,4-di-MeO-C_6H_3-
d	3-Br-4-MeO-C_6H_3-

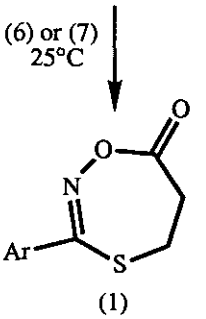


Table 1 Preparation of **1** and **4**

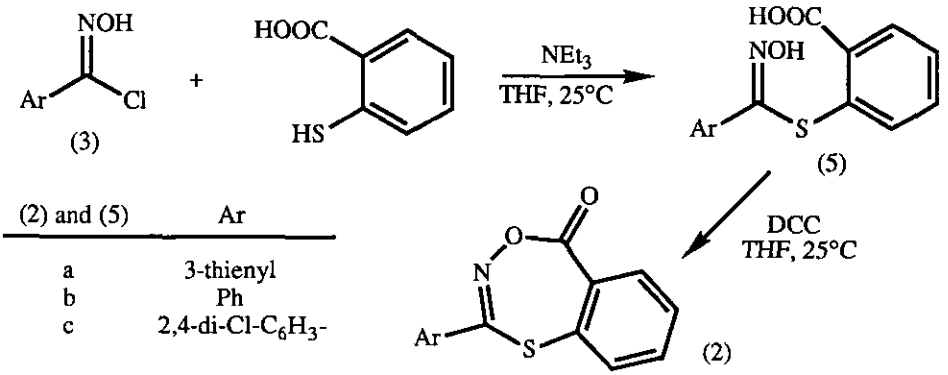
Compound	Melting point (°C)	Yield (%)	Diimide used for cyclization
(4a)	111-112	79	—
(4b)	142-144[A]	80	—
(4c)	119-121	66	—
(4d)	100-101	85	—
(1a)	64-66	58[B]	(6)
(1b)	144-146	39[B]	(7)
(1c)	87-90	94[C]	(7)
(1d)	90-93	38[B]	(7)

[A] Lit.[4] mp 146°C.

[B] Yield after radial chromatography.

[C] Yield after trituration with ether.

When thiosalicylic acid was reacted with the hydroximoyl chloride (**3**) using the procedure described above, the corresponding oxime acid (**5a-c**) was obtained and used without further purification (Table 2). The ^{1}H nmr spectra[7] of the oxime acids (**5a-c**) showed a broad exchangeable singlet for the oxime and acid protons between δ 9.5-10.5 and a carbonyl stretch in the infrared spectra[7] of 1680-1690 cm^{-1}, as well as broad, strong bands around 3200 cm^{-1} due to the hydroxyl group(s). The oxime acid (**5a-c**) was cyclized using DCC (**6**) as described previously and recrystallization of the crude product from benzene/light petroleum afforded the 2-substituted 5H-4,1,3-benzoxathiazepin-5-one (**2a-c**) (Table 2).



(2) and (5)	Ar
a	3-thienyl
b	Ph
c	2,4-di-Cl-C_6H_3-

Table 2 Preparation of **2** and **5**

Compound	Melting point (°C)	Yield (%)	^{13}C nmr data[A] C=N, C=O
(5a)	110-111	82	144.5, 168.1
(5b)	97-98	95	149.7, 168.1
(5c)	121-122	98	149.0, 168.1
(2a)	129-132	53	167.1, 167.3[B]
(2b)	136-139	72	167.5, 173.0
(2c)	114-116	57	165.8, 171.5

[A] Values are in ppm, $CDCl_3$ solvent for **2**, $CDCl_3$/DMSO-d_6 for **5**.

[B] The assignment is tentative.

The benzoxathiazepinones (**2a-c**) showed no exchangeable protons in the ^1H nmr spectra[8] and an increase in the frequency of the carbonyl stretch in the infrared spectra[8] to 1715-1725 cm^{-1}, consistent with ring closure, as were the ^{13}C nmr spectra (Table 2) and mass spectra.[8]

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REFERENCES

1. K. C. Liu, B. R. Shelton, and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916.

2. M. Masaki, H. Matsukubo, K. Masuzawa, Y. Chigira, and M. Ohta, *J. Heterocycl. Chem.*, 1965, **2**, 376.

3. H. Ulrich, 'Chemistry of Imidoyl Halides,' Plenum, New York, 1968, p. 165.

4. M. H. Benn, *Can. J. Chem.*, 1964, **42**, 2393.

5. Spectral data for compounds (**4a-d**). **4a**; Ir (KBr) ν_{max} 3270, 2550, 1715 cm^{-1}. ^1H Nmr ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.45 (2H, t, J = 8 Hz, CH_2COOH), 3.15 (2H, t, J = 8 Hz, SCH_2), 6.90 (1H, dd, J = 4 and 6 Hz, thienyl H4), 7.20 (1H, d, J = 6 Hz, thienyl H5), 7.30 (1H, d, J = 4 Hz, thienyl H3), 10.20 (2H, bs, NOH and COOH). ^{13}C Nmr ($CDCl_3$/DMSO-d_6, 50.3 MHz) δ 27.1 (SCH_2), 34.7 (CH_2COOH), 126.7, 126.8 and 128.0 (thienyl C3, C4 and C5), 138.1 (thienyl C2), 144.0 (C=NOH), 173.3 (COOH). Ci-ms m/z (%) 232 (M+1, 47), 126 (100). High res.-ms m/z 232.009, calcd for $C_8H_{10}NO_3S_2$,

232.010. **4b:** Ir (KBr) ν_{max} 3295, 2550, 1705 cm^{-1}. ^1H Nmr ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.30 (2H, t, J = 8 Hz, CH_2COOH), 2.80 (2H, t, J = 8 Hz, SCH_2), 7.20-7.50 (5H, m, aromatic protons), 10.80 (2H, bs, NOH and COOH). ^{13}C Nmr ($CDCl_3$/DMSO-d_6, 50.3 MHz) δ 26.2 (SCH_2), 34.5 (CH_2COOH), 128.1 and 128.2 (phenyl C2, C3, C5 and C6), 129.0 (phenyl C4), 133.6 (phenyl C1), 151.8 (C=NOH), 172.9 (COOH). Ci-ms m/z (%) 226 (M+1, 4), 104 (100). **4c:** Ir (KBr) ν_{max} 3250, 2550, 1695 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.50 (2H, t, J = 8 Hz, CH_2COOH), 2.95 (2H, t, J = 8 Hz, SCH_2), 3.80 (3H, s, MeO), 3.85 (3H, s, MeO), 6.85 (1H, d, J = 9 Hz, aromatic H5), 6.95 (1H, d, J = 3 Hz, aromatic H2), 7.05 (1H, dd, J = 3 and 9 Hz, aromatic H6), 10.70 (2H, bs, NOH and COOH). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 26.7 (SCH_2), 34.7 (CH_2COOH), 56.0 (3-MeO and 4-MeO), 111.1 (aromatic C2 and C5), 121.6 (aromatic C6), 125.1 (aromatic C1), 149.0, 150.6 and 154.9 (aromatic C3, C4 and C=NOH), 176.4 (COOH). Ci-ms m/z (%) 286 (M+1, 3), 164 (100). High res.-ms m/z 286.074, calcd for $C_{12}H_{16}NO_5S$, 286.075. **4d:** Ir (film) ν_{max} 3240, 2550, 1715 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.55 (2H, t, J = 8 Hz, CH_2COOH), 3.00 (2H, t, J = 8 Hz, SCH_2), 3.90 (3H, s, MeO), 6.90 (1H, d, J = 9 Hz, aromatic H5), 7.45 (1H, dd, J = 3 and 9 Hz, aromatic H6), 7.70 (1H, d, J = 3 Hz, aromatic H2), 10.40 (2H, bs, NOH and COOH). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 26.7 (SCH_2), 34.7 (CH_2COOH), 56.4 (MeO), 111.8 (aromatic C3 and C5), 126.4 (aromatic C1), 128.9 and 133.2 (aromatic C2 and C6), 153.0 and 157.3 (aromatic C4 and C=NOH), 176.4 (COOH). Ci-ms m/z (%) 334/336 (M+1, 10/8), 212 (100). High res.-ms m/z 333.976, calcd for $C_{11}H_{13}NO_4BrS$, 333.975.

6. Spectral data for compounds (**1a-d**). **1a:** Ir (KBr) ν_{max} 1770 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.75 (2H, t, J = 7 Hz, CH_2COON), 3.25 (2H, t, J = 7 Hz, SCH_2), 7.10-7.50 (3H, m, thienyl protons). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 28.3 (SCH_2), 33.4 (CH_2COON), 127.8, 130.2 and 131.2 (thienyl C3, C4 and C5), 133.0 (thienyl C2), 157.5 (C=N), 168.0 (C=O). Ci-ms m/z (%) 214 (M+1, 4), 89 (100). High res.-ms m/z 213.997, calcd for $C_8H_8NO_2S_2$, 213.999. **1b:** Ir (KBr) ν_{max} 1765 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.55 (2H, t, J = 7 Hz, CH_2COON), 2.85 (2H, t, J = 7 Hz, SCH_2), 7.40 (5H, m, aromatic protons). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 27.0 (SCH_2), 33.3 (CH_2COON), 128.8 and 129.0 (phenyl C2, C3, C4, C5 and C6), 130.8 (phenyl C1), 165.4 and 167.7 (C=N and C=O). Ci-ms m/z (%) 208 (M+1, 7), 73 (100). High res.-ms m/z 208.043, calcd for $C_{10}H_{10}NO_2S$, 208.043. **1c:** Ir (KBr) ν_{max} 1765 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.55 (2H, t, J = 7 Hz, CH_2COON), 2.90 (2H, t, J = 7 Hz, SCH_2), 3.85 (6H, s, 3-MeO and 4-MeO), 6.80-7.10 (3H, m, aromatic protons). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 27.2 (SCH_2), 33.2 (CH_2COON), 55.9 (3-MeO and 4-MeO), 111.0 and 111.4 (aromatic C2 and C5), 122.0 (aromatic C6), 123.0 (aromatic C1), 149.0 and 151.0 (aromatic C3 and C4), 165.0 and 168.0 (C=N and C=O). Ci-ms m/z (%) 268 (M+1, 8), 164 (100). High res.-ms m/z 268.065, calcd for $C_{12}H_{14}NO_4S$, 268.064. **1d:** Ir (KBr) ν_{max} 1770 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 2.65 (2H, t, J = 7 Hz, CH_2COON), 3.00 (2H, t, J = 7 Hz, SCH_2), 3.90 (3H, s, MeO), 6.95 (1H, m, aromatic H5), 7.45 (1H, m, aromatic H6), 7.75 (1H, m, aromatic H2). ^{13}C Nmr ($CDCl_3$, 50.3 MHz) δ 27.4

(SCH_2), 33.3 (CH_2COON), 56.5 (MeO), 111.9 and 112.1 (aromatic C3 and C5), 124.5 (aromatic C1), 129.6 and 133.5 (aromatic C2 and C6), 157.9 (aromatic C4), 163.0 (C=N), 167.8 (C=O). Ci-ms m/z (%) 316/318 (M+1, 7/8), 212 (100). High res.-ms m/z 315.963, calcd for $C_{11}H_{11}NO_3BrS$, 315.964.

7. Spectral data for compounds (**5a-c**). **5a:** Ir (KBr) ν_{max} 3200, 1680 cm^{-1}. ^1H Nmr ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.10-7.25 (4H, m, thienyl H5 and thiosalicylic ring H3, H4 and H5), 7.40 (1H, d, J = 5 Hz, thienyl H4), 7.60 (1H, d, J = 3 Hz, thienyl H2), 7.95 (1H, dd, J = 2 and 7.5 Hz, thiosalicylic ring H6), 10.40 (2H, bs, NOH and COOH). Ci-ms m/z (%) 280 (M+1, 2.6), 110 (100). **5b:** Ir (KBr) ν_{max} 3100, 1690 cm^{-1}. ^1H Nmr ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.00-7.40 (6H, m, phenyl H3, H4 and H5 and thiosalicylic ring H3, H4 and H5), 7.65 (2H, m, phenyl H2 and H6), 7.90 (1H, m, thiosalicylic ring H6), 11.50 (2H, bs, NOH and COOH). Ci-ms m/z (%) 274 (M+1, 6), 104 (100). High res.-ms m/z 274.056, calcd for $C_{14}H_{12}NO_3S$, 274.054. **5c:** Ir (KBr) ν_{max} 3240, 1690 cm^{-1}. ^1H Nmr ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.00 (1H, ddd, J = 1, 2 and 8 Hz, thiosalicylic ring H3), 7.15-7.40 (5H, m, dichlorophenyl ring H3, H5 and H6 and thiosalicylic ring H4 and H5), 7.50 (1H, m, thiosalicylic ring H6), 10.80 (2H, bs, NOH and COOH). Ci-ms m/z (%) 342 (M+1, 1.3), 188 (100).

8. Spectral data for compounds (**2a-c**). **2a:** Ir (KBr) ν_{max} 1715 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 7.35-7.60 (5H, m, thienyl H4 and H5 and thiosalicylic ring H3, H4 and H5), 8.00 (1H, m, thiosalicylic ring H6), 8.20 (1H, d, J = 2.5 Hz, thienyl H2). Ci-ms m/z (%) 262 (M+1, 8), 153 (100). High res.-ms m/z 262.000, calcd for $C_{12}H_8NO_2S_2$, 262.000. **2b:** Ir (KBr) ν_{max} 1725 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 7.40-7.65 (6H, m, phenyl H3, H4 and H5 and thiosalicylic ring H3, H4 and H5), 8.00 (3H, m, phenyl H2 and H6 and thiosalicylic ring H6). Ci-ms m/z (%) 256 (M+1, 1.5), 104 (100). High res.-ms m/z 256.040, calcd for $C_{14}H_{10}NO_2S$, 256.043. **2c:** Ir (KBr) ν_{max} 1720 cm^{-1}. ^1H Nmr ($CDCl_3$, 200 MHz) δ 7.25-7.55 (6H, m, dichlorophenyl ring H3, H5 and H6 and thiosalicylic ring H3, H4 and H5), 8.05 (1H, m, thiosalicylic ring H6). Ci-ms m/z (%) 324/326 (M+1, 1.8/1.6), 172 (100). High res.-ms m/z 323.966, calcd for $C_{14}H_8NO_2Cl_2S$, 323.965.

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