A CONVENIENT SYNTHESIS OF 3-HETEROARYLTHIOMETHYL-1H,8H-CYCLOHEPTA[d]PYRAZOL-8-ONES

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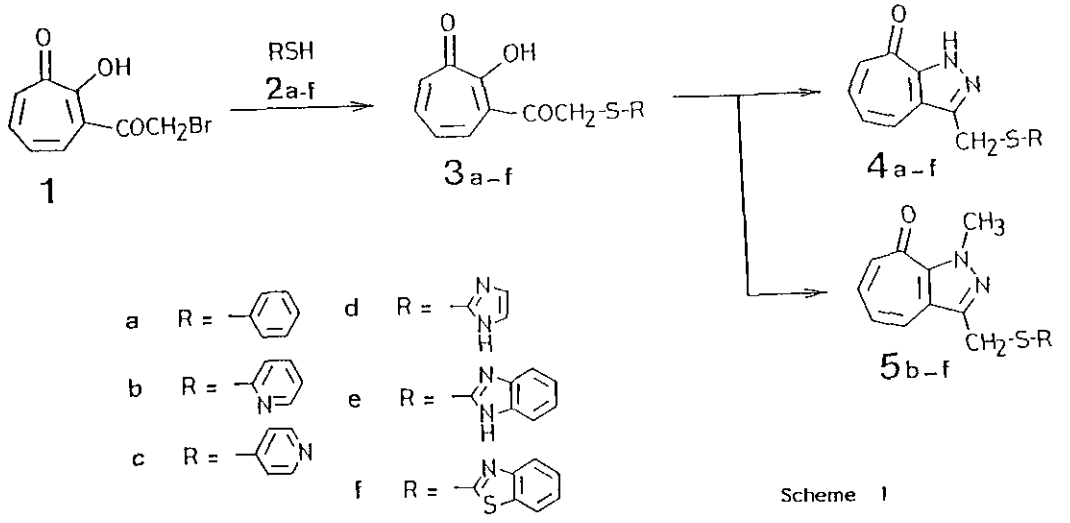
Abstract — The reactions of 3-(bromoacetyl)tropolone (1) with benzenethiol (2a) and heteroarenethiols (2b-f) gave 3-[(phenylthio)acetyl]tropolone (3a) and 3-[(heteroarylthio)acetyl]tropolones (3b-f), respectively. These compounds (3a-f) reacted with hydrazine hydrate and methylhydrazine to afford 3-phenylthiomethyl- (4a) and 3-heteroarylthiomethyl-1H,8H-cyclohepta[d]pyrazol-8-ones (4b-f) and their corresponding 1-methyl substituted compounds (5b-f), respectively.

For many years, we have engaged in the synthesis of heterocycle-fused troponoids from 3-acetyltropolone. Recently, gastric antisecreting effect has been found in 2-(heteroarylmethylthio)cycloheptimidazoles and their S-oxides,[2] which have the five-membered diazaheterocycle-fused tropoid structure. On the other hand, their partial structure is very similar to that of omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole,[3] which is undergoing the clinical trial as an anti-ulcer agent. In order to obtain biologically more active heterocycle-fused non-benzenoid aromatic compounds, we introduced heteroarylthiomethyl group into the 3-position of 1H,8H-cyclohepta[d]pyrazol-8-one. This paper deals with these results.

It is well-known that treatment of α-haloketones with thiols gives α-alkylthio or α-arylthio ketones.[4] A mixture of 3-(bromoacetyl)tropolone (1)[5] and benzenethiol (2a) in absolute ethanol was refluxed for 30 min to give 3-[(phenylthio)acetyl]tropolone (3a) in 48% yield. Heteroarenethiols (2b-f) also reacted

with the α-bromoketone (1) to afford the corresponding 3-[(heteroarylthio)acetyl]tropolones (3b-f) in 51-87% yields. Heating of these compounds (3a-f) with hydrazine hydrate for 1 h in methanol gave 3-phenylthiomethyl- (4a) and 3-heteroarylthiomethyl-1H,8H-cyclohepta[d]pyrazol-8-ones (4b-f) in 21-76% yields. In a similar manner, the reaction of the compounds (3b-f) with methylhydrazine gave 3-heteroarylthiomethyl-1-methyl derivatives (5b-f) in 20-32% yields. The procedure in this work provides a simple and convenient method for the preparation of a series of biologically active 3-heteroarylthiomethyl substituted 1H,8H-cyclohepta[d]pyrazol-8-ones.



Scheme 1

EXPERIMENTAL

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer. The ^{1}H nmr spectra were recorded with a JEOL JNM-PMX60SI spectrometer (60 MHz). The mass spectra were measured on a JEOL JMX-DX303HF spectrometer.

3-[(Phenylthio)acetyl]- (3a) and 3-[(Heteroarylthio)acetyl]tropolones (3b-f); General Procedure:

A solution of 3-(bromoacetyl)tropolone (1) (1.22 g, 5.0 mmol) and benzenethiol (2a) or heteroarenethiol (2b-f) (5.0 mmol) in absolute ethanol (40 ml) was refluxed for 30 min. After cooling, the precipitates were collected and recrystallized from ethanol to give 3a or 3b-f.

3-[(Phenylthio)acetyl]tropolone (3a). Yellow prisms (from EtOH); yield 631 mg (48%); mp 106-107 °C; ir ($CHCl_3$) ν 3125 (OH), 1695 (C=O), 1620 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.41 (2H, s, CH_2), 6.81-7.78 (10H, m); ms m/z 272 (M^+). Anal. Calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 66.10; H, 4.57.

3-[(2-Pyridylthio)acetyl]tropolone (3b). Yellow prisms (from EtOH); yield 919 mg (64%); mp 180-183 °C; ir ($CHCl_3$) ν 3424 (OH), 1686 (C=O), 1600 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 5.20 (2H, s, CH_2), 7.10-8.06 (9H, m); ms m/z 273 (M^+). Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.13. Found: C, 61.35; H, 4.34; N, 5.32.

3-[(4-Pyridylthio)acetyl]tropolone (3c). Yellow prisms (from EtOH); yield 1.26 g (87%); mp 223-225 °C; ir ($CHCl_3$) ν 3664 (OH), 1747 (C=O), 1589 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.87 (2H, s, CH_2), 6.30-8.07 (5H, m), 7.85 (2H, d, J = 6 Hz, H-3', H-5'), 8.65 (2H, d, J = 6 Hz, H-2', H-6'); ms m/z 273 (M^+). Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.13. Found: C, 61.49; H, 4.07; N, 5.41.

3-[(2-Imidazolylthio)acetyl]tropolone (3d). Yellow prisms (from EtOH); yield 1.10 g (81%); mp 190-192 °C; ir ($CHCl_3$) ν 3320 (OH), 3108 (NH), 1661 (C=O), 1591 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.85 (2H, s, CH_2), 7.11-8.15 (8H, m); ms m/z 262 (M^+). Anal. Calcd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68. Found: C, 54.65; H, 4.11; N, 10.92.

3-[(2-Benzimidazolylthio)acetyl]tropolone (3e). Yellow prisms (from EtOH); yield 1.40 g (87%); mp 180-183 °C; ir ($CHCl_3$) ν 3424 (OH), 3104 (NH), 1686 (C=O), 1600 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 5.20 (2H, s, CH_2), 7.10-8.06 (10H, m); ms m/z 312 (M^+). Anal. Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.52; H, 3.87; N, 8.97. Found: C, 61.56; H, 3.98; N, 9.27.

3-[(2-Benzothiazolylthio)acetyl]tropolone (3f). Yellow prisms (from EtOH); yield 777 mg (51%); mp 86-88 °C; ir ($CHCl_3$) ν 3125 (OH), 1705 (C=O), 1620 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.78 (2H, s, CH_2), 6.77-7.91 (8H, m), 8.55 (1H, br, OH); ms m/z 329 (M^+). Anal. Calcd for $C_{16}H_{11}NO_3S_2$: C, 58.34; H, 3.37; N, 4.25. Found: C, 58.21; H, 3.53; N, 4.28.

3-Phenylthiomethyl- (4a) and 3-Heteroarylthiomethyl-1H,8H-cyclohepta[d]pyrazol-8-ones (4a-f); General Procedure:

A solution of 3-[(phenylthio)acetyl]- (3a) or 3-[(heteroarylthio)acetyl]tropolone (3b-f) (2.5 mmol) and 100% hydrazine hydrate (250 mg, 5.0 mmol) in methanol (10ml) was refluxed for 1 h. After removal of the solvent, the residue was recrystallized to give 4a and 4b-f.

3-Phenylthiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (4a). Orange prisms (from EtOH); yield 175 mg (27%); mp 117-118 °C; ir ($CHCl_3$) ν 3180 (NH), 1630 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.46 (2H, s, CH_2), 6.40-7.80 (10H, m); ms m/z 268 (M^+). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 66.98; H, 4.73; N, 10.56.

3-(2-Pyridylthio)methyl-1H,8H-cyclohepta[d]pyrazol-8-one (4b). Light orange prisms (from benzene);

yield 405 mg (59%); mp 159-160 °C; ir ($CHCl_3$) ν 3148 (NH), 1626 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.87 (2H, s, CH_2), 6.63-8.10 (8H, m), 8.50 (1H, dd, J = 5, 2 Hz, H-6'); ms m/z 269 (M^+). Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.71; H, 4.41; N, 15.53.

3-(4-Pyridylthio)methyl-1H,8H-cyclohepta[d]pyrazol-8-one (4c). Orange prisms (from benzene); yield 152 mg (21%); mp 193-194 °C; ir ($CHCl_3$) ν 3150 (NH), 1620 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.63 (2H, s, CH_2), 6.30-7.90 (5H, m), 7.37 (2H, d, J = 6 Hz, H-3', H-5'), 8.42 (2H, d, J = 6 Hz, H-2', H-6'); ms m/z 269 (M^+). Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.19; H, 4.34; N, 15.56.

3-(2-Imidazolyl)thiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (4d). Orange prisms (from benzene); yield 135 mg (21%); mp 189-190 °C; ir ($CHCl_3$) ν 3150 (NH), 1626 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.54 (2H, s, CH_2), 6.44-7.67 (8H, m); ms m/z 258 (M^+). Anal. Calcd for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 56.12; H, 4.08; N, 21.75.

3-(2-Benzimidazolyl)thiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (4e). Orange prisms (from EtOH); yield 478 mg (62%); mp 198-199 °C; ir ($CHCl_3$) ν 3156 (NH), 1622 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.91 (2H, s, CH_2), 6.71-8.06 (10H, m); ms m/z308 (M^+). Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found: C, 62.17; H, 4.20; N, 17.89.

3-(2-Benzothiazolyl)thiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (4f). Orange prisms (from benzene); yield 608 mg (76%); mp 197-199 °C; ir ($CHCl_3$) ν 3170 (NH), 1635 cm-^{1} (C=O); ^1H nmr ($CDCl_3$) δ 4.99 (2H, s, CH_2), 6.63-8.20 (9H, m); ms m/z 325 (M^+). Anal. Calcd for $C_{16}H_{11}N_3OS_2$: C, 59.06; H, 3.41; N, 12.91. Found: C, 59.26; H, 3.50; N, 13.00.

3-Heteroarylthiomethyl-1-methyl-1H,8H-cyclohepta[d]pyrazol-8-ones (5b-f); General Procedure:
A solution of 3-[(heteroarylthio)acetyl]tropolone (3b-f) (1.0 mmol) and methylhydrazine (92 mg, 2.0 mmol) in methanol (10 ml) was refluxed for 2 h. After removal of the solvent, the residue was separated by preparative thin layer chromatography [Wakogel B-10 (35 g) on 30 x 30 cm] with ethyl acetate and the major product was recrystallized to give 5b-f.

1-Methyl-3-(2-pyridyl)thiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (5b). Light orange prisms (from hexane); yield 84 mg (30%); mp 98-99 °C; ir ($CHCl_3$) ν 1633 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.40 (3H, s, CH_3), 4.73 (2H, s, CH_2), 6.37-7.77 (7H, m), 8.49 (1H, dd, J = 5, 2 Hz, H-6'); ms m/z 283 (M^+). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.35; H, 4.70; N, 14.71.

1-Methyl-3-(4-pyridyl)thiomethyl-1H,8H-cyclohepta[d]pyrazol-8-one (5c). Light brown prisms (from benzene); yield 74 mg (25%); mp 135-136 °C; ir ($CHCl_3$) ν 1638 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.20 (3H, s, CH_3), 4.76 (2H, s, CH_2), 6.30-7.46 (4H, m), 7.09 (2H, d, J = 6 Hz, H-3', H-5'), 8.29 (2H, d, J = 6 Hz, H-2', 6'); ms m/z 283 (M^+). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found:

C, 63.71; H, 4.67; N, 15.02.

3-(2-Imidazolyl)thiomethyl-1-methyl-1H,8H-cyclohepta[d]pyrazol-8-one (5d). Brown prisms (from MeOH); yield 77 mg (29%); mp 157-160 °C; ir ($CHCl_3$) ν 3125 (NH), 1633 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.30 (3H, s, CH_3), 4.52 (2H, s, CH_2), 6.50-7.56 (7H, m); ms m/z 272 (M^+). Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.33; H, 4.44; N, 20.58. Found: C, 57.07; H, 4.25; N, 20.81.

3-(2-Benzimidazolyl)thiomethyl-1-methyl-1H,8H-cyclohepta[d]pyrazol-8-one (5e). Orange prisms (from benzene); yield 61 mg (20%); mp 107-108 °C; ir ($CHCl_3$) ν 3150 (NH), 1630 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.61 (3H, s, CH_3), 5.22 (2H, s, CH_2), 6.84-8.21 (9H, m); ms m/z 322 (M^+). Anal. Calcd for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38. Found: C, 63.12; H, 4.61; N, 17.52.

3-(2-Benzothiazolyl)thiomethyl-1-methyl-1H,8H-cyclohepta[d]pyrazol-8-one (5f). Orange prisms (from benzene); yield 119 mg (32%); mp 129-130 °C; ir ($CHCl_3$) ν 1625 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 4.72 (3H, s, CH_3), 5.22 (2H, s, CH_2), 6.76-8.29 (8H, m); ms m/z 339 (M^+). Anal. Calcd for $C_{17}H_{13}N_3OS_2$: C, 60.15; H, 3.86; N, 12.38. Found: C, 59.94; H, 3.91; N, 12.28.

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