Transformation of Pyrazolo[4,3-*c*]isothiazoles into 3,4-Disubstituted 1,2-Isothiazoles

Taisei Ueda, Yoshitsugu Shibata and Jinsaku Sakakibara*

Faculty of Pharmaceutical Sciences, Nagoya City University,
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

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Pyrazolo[4,3-*c*]isothiazoles **4** and **5** were synthesized by the reaction of 4-aminoantipyrine **1** with thionyl chloride. Treatment of **4** or **5** with alkylamines underwent pyrazole ring opening to afford 3,4-disubstituted 1,2-isothiazoles **8a-f**.

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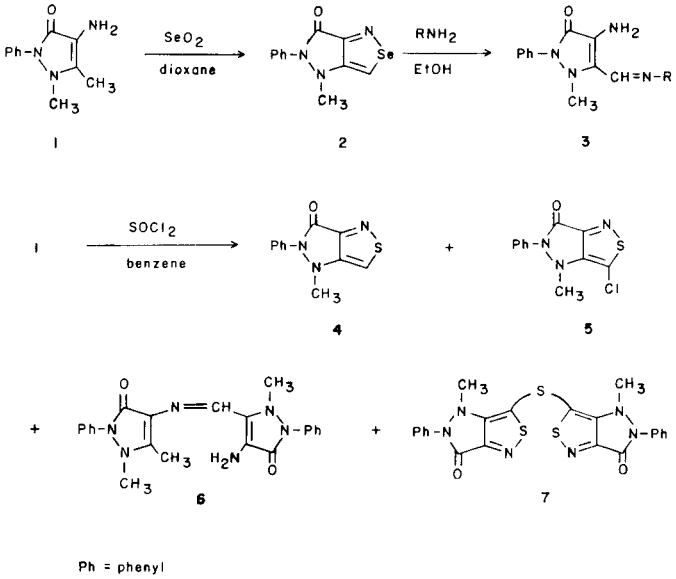
Previously we reported the facile conversion of *C*-methyl group of 4-aminoantipyrine **1** to alkyliminomethyl group by way of the formation of pyrazolo[4,3-*c*]isoselenazole **2** followed by the reaction with primary alkylamines [1]. Such a finding induced our interest to synthesize 4,5-dihydro-4-methyl-6-oxo-5-phenyl-6*H*-pyrazolo[4,3-*c*]isothiazole **4** and 4,5-dihydro-3-chloro-4-methyl-6-oxo-5-phenyl-6*H*-pyrazolo[4,3-*c*]isothiazole **5** which are analogues of **2** and investigate their reactivities towards various alkylamines. During the investigation we have found a facile transformation of pyrazolo[4,3-*c*]isothiazoles **4**, **5** into 3,4-disubstituted 1,2-isothiazoles **8a-f** by the reaction with alkylamines, which we report in this paper.

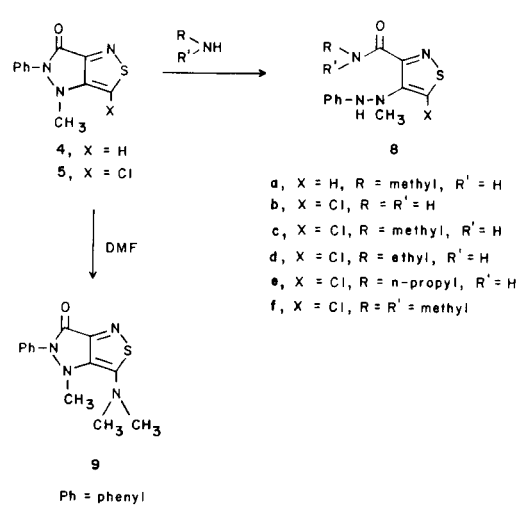
Compounds **4**, **5** which are novel heterocycles were readily available by the reaction of **1** with thionyl chloride [2] in refluxing benzene and were accompanied by two by-products 4-(4-amino-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-methylideneamino)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one **6** and bis[3-(4-methyl-6-oxo-5-phenylisothiazolo[4,3-*c*]-pyrazolyl)]sulfide **7**. The structures of these products **4**, **5**, **6** and **7** were established by their ir, proton nmr, and mass spectra as well as by analytical data. The reactivity of **4** or **5** towards alkylamines was investigated as follows: The initial treatment of **4** or **5** with alkylamines, such as methylamines, ethylamine, *n*-propylamine, allylamine, and *sec*-butylamine in refluxing ethanol did not proceed. However, the reaction of **4** or **5** with a large excess of alkylamines in a sealed tube at 100° for 16 hours underwent pyrazole ring opening to give 3-alkylcarbamoyl-5-substituted-4-(*N*-methyl-*N'*-phenylhydrazino)-1,2-isothiazoles **8a-f**. The ir spectra of compounds **8a-f** showed absorptions due to phenylhydrazino and amido groups (NNHPh, CONH or $CONH_2$) in the region of 3200-3400 cm^{-1}. The proton nmr spectrum of **8a** disclosed the absorption of unchanged isothiazole ring C_3-proton at δ 8.04 ppm. Mass spectra and elemental analyses were consistent with assigned structures (Table I). As described above chloro group of **5** was not displaced by alkylamino group. However, when **5** and dimethylformamide (DMF) were heated in a sealed tube at 100° for 16 hours, dimethylamino group was introduced easily to give 4,5-dihydro-3-dimethylamino-4-methyl-6-oxo-5-phenyl-6*H*-pyrazolo[4,3-*c*]isothiazole **9** in 52% yield [3].

Scheme 1



Ph = phenyl

Scheme 2



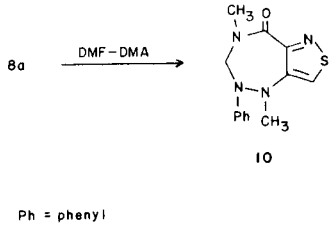
Ph = phenyl

Table I

3-Alkylcarbamoyl-5-substituted-4-(*N*-methyl-*N'*-phenylhydrazino)-1,2-isothiazoles **8**

Compound No.	Yield (%)	Mp °C	Molecular Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
8a	53	90-92	$C_{12}H_{14}N_4OS$ 262.34	54.94	5.38	21.36	54.90	5.24	21.57
8b	10	146-147	$C_{11}H_{11}ClN_4OS$ 282.75	46.73	3.92	19.81	47.01	3.70	19.53
8c	36	73-76	$C_{12}H_{13}ClN_4OS$ 296.78	48.57	4.42	18.88	48.52	4.21	18.65
8d	68	60-61	$C_{13}H_{15}ClN_4OS$ 310.81	50.24	4.87	18.03	50.33	4.83	18.00
8e	37	70-71	$C_{14}H_{17}ClN_4OS$ 324.83	51.77	5.28	17.25	51.61	5.18	17.34
8f	34	60-61	$C_{13}H_{15}ClN_4OS$ 310.81	50.24	4.87	18.03	49.98	4.58	17.80

Scheme 3



10

Ph = phenyl

We thought the above obtained isothiazoles **8** might be useful as intermediates for the synthesis of further annelated compounds. Thus the reaction of **8a** and *N,N*-dimethylformamide dimethylacetal (DMF-DMA) was examined [4] to give 4,7-dimethyl-8-oxo-5-phenyl-4,5,6,7-tetrahydro-8*H*-isothiazolo[4,3-**e**][1,2,4]triazepin **10** in 27% yield. The proton nmr spectrum of **10** revealed an N-CH_2-N function at δ 5.08 ppm. Elemental analysis and mass spectrum [m/z 274 (M^+)] established the assigned structure.

Consequently our new method to synthesize 3,4-disubstituted isothiazoles is convenient and useful for the synthesis of further annelated compounds which may show important pharmacological activities [5].

EXPERIMENTAL

The melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were measured with an IR-810 machine from Nihon Bunko Spectroscopic Co. Ltd. Mass spectra were measured with a Japan Electron Optics Laboratory Co., JMS-DX 300 mass spectrometer. The proton nmr spectra were recorded with a Japan Electron Optics Laboratory Co. JNM-MH-100 Spectrometer using tetramethylsilane as internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad.

Reaction of 4-Aminoantipyrine with Thionyl Chloride.

A solution of 1.77 g (15 mmoles) of thionyl chloride in 20 ml of benzene was added dropwise to a solution of 1 g (5 mmoles) of 4-aminoantipyrine in 100 ml of benzene. The mixture was refluxed for 4 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel.

The first chloroform eluate was collected and chloroform was distilled off. The residue was recrystallized from ethanol to give **5**, yield 227 mg (17%), mp 126-127°; ir (potassium bromide): ν 1680 cm^{-1} (C=O); ms: m/z 265 (M^+), 267 (M+2); ^{1}H-nmr (deuteriochloroform): δ 3.14 (3H, s, N-CH_3), 7.21-7.72 (5H, m, Ar).

Table II

Spectral Data of Compounds **8**

Compound No.	IR (cm^{-1})	^{1}H-NMR (δ ppm) [a]
8a	3300 (NHPh), 3250 (CONH), 1645 (C=O)	2.90 (3H, d, NH-CH_3), 3.20 (3H, s, N-CH_3), 6.62-7.30 (7H, m, Ar, CONH, N*H*Ph), 8.04 (1H, s, =CH-S-)
8b	3330, 3260 (NH_2), 3200 (NHPh), 1650 (C=O)	3.00 (3H, s, N-CH_3), 6.56-7.24 (5H, m, Ar), 7.40 (2H, br, $CONH_2$), 7.50 (1H, br, N*H*Ph)
8c	3370 (NHPh), 3200 (CONH), 1660 (C=O)	2.95 (3H, d, NH-CH_3), 3.00 (3H, s, N-CH_3), 6.50-7.22 (5H, m, Ar), 7.25 (1H, br, NHCO), 7.49 (1H, br, N*H*Ph)
8d	3370 (NHPh), 3200 (CONH), 1660 (C=O)	1.25 (3H, t, CH_2CH_3), 3.00 (3H, s, N-CH_3), 3.48 (2H, q, CH_2CH_3), 6.60-7.25 (5H, m, Ar), 7.30 (1H, br, CONH), 7.52 (1H, s, N*H*Ph)
8e	3370 (NHPh), 3200 (CONH), 1660 (C=O)	0.96 (3H, t, $CH_2CH_2CH_3$), 1.62 (2H, m, $CH_2CH_2CH_3$), 3.00 (3H, s, N-CH_3), 3.38 (2H, q, $CH_2CH_2CH_3$), 6.60-7.28 (5H, m, Ar), 7.32 (1H, br, CONH), 7.50 (1H, s, N*H*Ph)
8f	3370 (NHPh), 1670 (C=O)	2.80 (3H, s, N-CH_3), 3.07 (3H, s, N-CH_3), 3.11 (3H, s, N-CH_3), 6.00 (1H, s, N*H*Ph), 6.64-7.26 (5H, m, Ar)

[a] Solvent: deuteriochloroform.

Anal. Calcd. for $C_{11}H_8ClN_3OS$: C, 49.72; H, 3.03; N, 15.81. Found: C, 49.73; H, 2.93; N, 15.73.

The second eluate gave **4** by the similar work-up to the above procedure, yield 138 mg (12%), mp 123-125°; ir (potassium bromide): 1685 cm^{-1} (C=O); ms: m/z 231 (M^+); ^{1}H-nmr (deuteriochloroform): δ 3.28 (3H, s, N-CH_3), 7.28-7.78 (5H, m, Ar), 8.21 (1H, s, =CH-).

Anal. Calcd. for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18.17. Found: C, 57.10; H, 3.71; N, 18.30.

The third eluate gave **6** by the similar work-up to the above procedure, yield 125 mg (13%), mp 230-233°; ir (potassium bromide): 3330, 3260 cm^{-1} (NH_2), 1630 cm^{-1} (C=O); ms: m/z 402 (M^+); ^{1}H-nmr (deuteriochloroform): δ 2.38 (3H, s, C-CH_3), 2.87 (3H, s, N-CH_3), 3.12 (3H, s, N-CH_3), 5.00 (2H, br, NH_2), 7.04-7.84 (10H, m, Ar), 9.70 (1H, s, =CH-).

Anal. Calcd. for $C_{22}H_{22}N_6O_2$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.60; H, 5.30; N, 20.86.

The fourth eluate gave **7** by the similar work-up to the above procedure, yield 310 mg (26%), mp 160-165°; ir (potassium bromide): 1685 cm^{-1} (C=O), ms: m/z 492 (M^+), 494 (M+2); ^{1}H-nmr (deuteriochloroform): δ 3.29 (6H, s, N-CH_3), 7.19-7.75 (10H, m, Ar).

Anal. Calcd. for $C_{22}H_{16}N_6S_3O_2$: C, 53.64; H, 3.27; N, 17.06. Found: C, 53.42; H, 3.21; N, 16.90.

Reaction of **4** or **5** with Alkylamines.

A mixture of 1 g of **4** or **5** and alkylamine (50 ml) was heated at 100° for 16 hours in a sealed tube. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform. The extract was dried and the solvent was removed off. The residue was purified by silica gel column chromatography and then recrystallized from ethanol (Table I).

4,5-Dihydro-3-dimethylamino-4-methyl-6-oxo-5-phenyl-6*H*-pyrazolo[4,3-*c*]-isothiazole **9**.

A solution of **5** (1g, 3.8 mmoles) in dimethylformamide (40 ml) was heated at 100° for 16 hours in a sealed tube. After cooling to room temperature solvent was removed off under reduced pressure and the residue was chromatographed on silica gel. The chloroform eluate was collected and the solvent was removed off. The residue was recrystallized from ethanol to yield 540 mg (52%) of **9**, mp 167-170°; ir (potassium bromide) ν max 1665 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.87 (3H, s, N-CH_3), 3.02 (6H, s, $N(CH_3)_2$), 7.10-7.81 (5H, m, Ar); ms: m/z 274(M^+).

Anal. Calcd. for $C_{13}H_{14}N_4OS$: C, 56.92; H, 5.14; N, 20.42. Found: C, 56.83; H, 4.93; N, 20.27.

4,7-Dimethyl-8-oxo-5-phenyl-4,5,6,7-tetrahydro-8*H*-isothiazolo[4,3-*e*]-[1,2,4]triazepin **10**.

A mixture of **8a** (1 g, 3.8 mmoles) and dimethylformamide dimethylacetal (3 ml) was refluxed for 3 hours. Excess dimethylformamide dimethylacetal was removed off under reduced pressure and the residue was chromatographed on silica gel. The chloroform eluate was collected and the solvent was removed off. The residue was recrystallized from ethanol to give colorless prisms of mp 149-150°, yield 277 mg (27%); ir (potassium bromide): ν max 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.16 (3H, s, N-CH_3), 3.22 (3H, s, N-CH_3), 5.08 (2H, s, N-CH_2-N), 6.72-7.36 (5H, m, Ar), 7.65 (1H, s, =CH-), ms: m/z 274(M^+).

Anal. Calcd. for $C_{13}H_{14}N_4OS$: C, 56.92; H, 5.14; N, 20.42. Found: C, 57.12; H, 5.02; N, 20.22.

Acknowledgement.

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