Neighboring Group Participation in Cyclodehydration. A Regiospecific Isoxazole Synthesis

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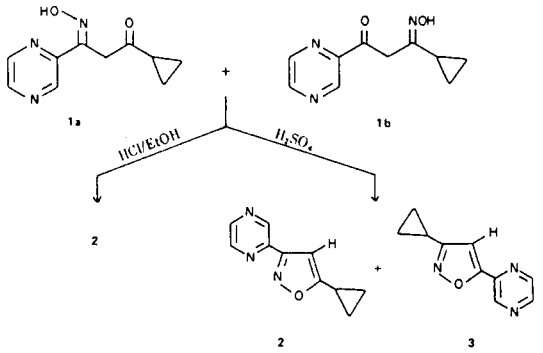
The regiospecific synthesis of isoxazoles **2**, **11**, **14**, and **15** is explained in terms of neighboring group participation of the *ortho* nitrogen of the heterocyclic ring in the cyclodehydration step.

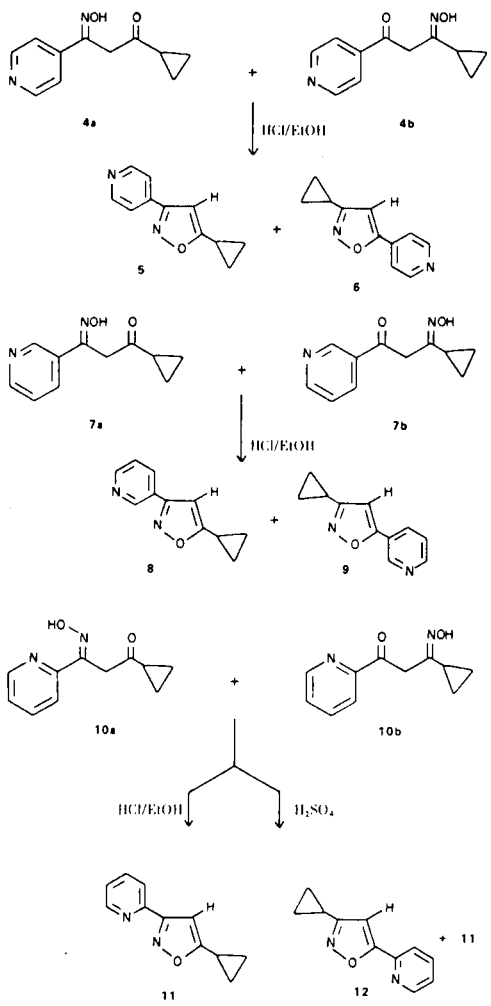
J. Heterocyclic Chem., 14, 531 (1977).

The synthesis of isoxazoles from unsymmetrical 1,3-dicarbonyl compounds *via* the intermediacy of an oxime frequently results in a mixture of two isomeric products, the ratio of which is dependent on the composition of the oxime precursors (1-3). We wish to report an isoxazole synthesis in which the isoxazole formed is independent of the original oxime mixture.

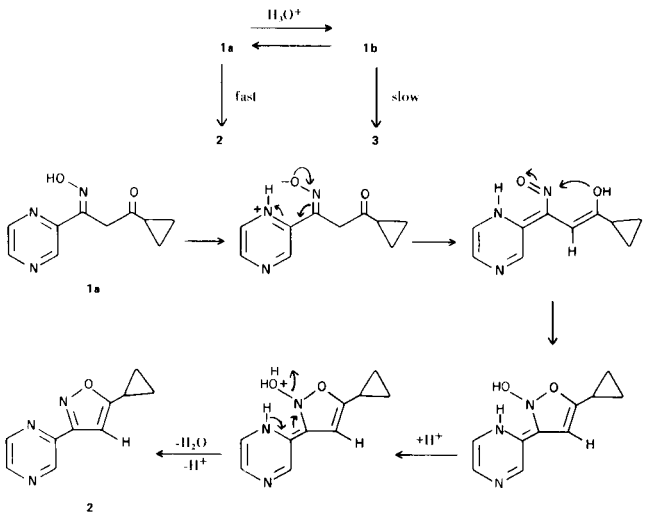
Cyclodehydration of a 50/50 mixture of the oximes **1a** and **1b** with concentrated sulfuric acid, resulted in approximately equal amounts of the isomeric isoxazoles **2** and **3** (4). Surprisingly, when an ethanol solution of this oxime mixture was heated 30 minutes with a catalytic amount of hydrochloric acid **2** was the only isoxazole formed (5). In addition, if the ethanol solution was stirred with hydrochloric acid at 0° for 5 minutes, work up gave a mixture containing **2** and equal amounts of **1a** and **1b**. It was further observed that when the isomeric series of



oxime mixtures **4a** and **4b**, **7a** and **7b**, and **10a** and **10b** were heated with a catalytic amount of hydrochloric acid as above, only the **10a** and **10b** mixture which contains an *ortho* nitrogen in the heterocyclic ring gave a single isoxazole product. Significantly longer heating time (3-4 hours), was required for complete conversion of the mixtures **4a** and **4b** and **7a** and **7b** to their respective isoxazole isomers. Treatment of the **10a** and **10b** mixture with sulfuric acid resulted in equal amounts of **11** and **12**. When any of the oxime mixtures were heated without acid only starting material was recovered (6).

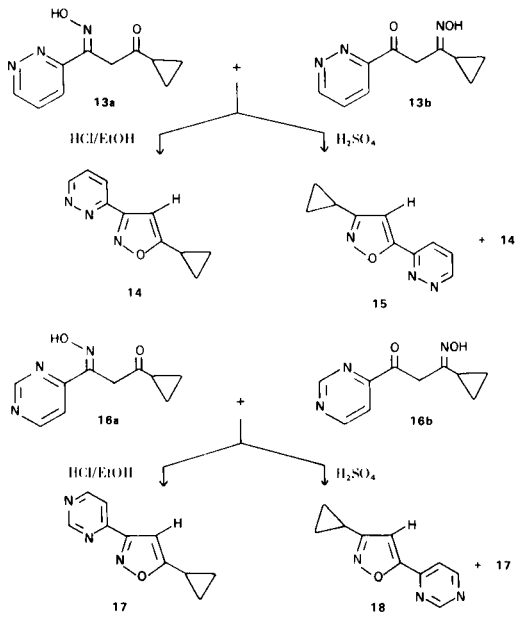


We wish to propose the following scheme as a possible explanation for the transformation of **1a** and **1b** to **2** under catalytic conditions.



In dilute acid compound **1a** undergoes cyclodehydration with assistance of the *ortho* nitrogen in the heterocyclic ring. In concentrated acid complete protonation of the heterocyclic ring prevents internal proton transfer from the oxime to the *ortho* nitrogen. Cyclodehydration under strongly acidic conditions leads *via* the normal mechanism to a mixture of isoxazoles that reflects the initial oxime isomer ratio.

This hypothesis is further supported by the observation that mixtures of the oximes **13a** and **13b**, and **16a** and **16b** gave only **14** and **17** respectively when subjected to catalytic conditions but gave the mixtures **14** and **15**, and **17** and **18** when sulfuric acid was used (7).



EXPERIMENTAL (8)

Catalytic Cyclodehydration. General Procedure -Table I.

A solution containing 0.01 mole of a 50/50 mixture of the monooximes of 1-cyclopropyl-3-(heterocyclic)-1,3-propanedione and 2 drops of 2 *N* hydrochloric acid in 35 ml. of ethanol was heated for 0.5 hour on a steam bath. The hot solution was poured over 200 g. of ice. Precipitates were filtered, washed with water and air dried. Oils were isolated, dissolved in ether and precipitated with hydrochloric acid.

Sulfuric Acid Cyclodehydration. General Procedure - Table I.

To a stirred solution of 0.02 mole of 1-cyclopropyl-3-(heterocyclic)-1,3-propanedione, 1- and 3-monooxime in 50 ml. of methylene chloride cooled to 0° was added dropwise over 15 minutes, 7.5 ml. of sulfuric acid maintaining the internal temperature below +10°. Following addition the reaction mixture was stirred at room temperature for 30 minutes and then poured onto cracked ice. The mixture was made basic with 10 *N* sodium hydroxide and the organic layer was separated and dried (magnesium sulfate). Removal of the solvent under reduced pressure gave an isomeric mixture of a cylcopropylisoxazolyl-heterocycle which was separated by partition chromatography.

1-Cyclopropyl-3-pyrazinyl-1,3-propanedione, 1- and 3-Monooxime (**1a** and **1b**). General Procedure.

A stirred mixture of 19.0 g. (0.1 mole) of 1-cyclopropyl-3-pyrazinyl-1,3-propanedione, 6.95 g. (0.1 mole) of hydroxylamine hydrochloride and 27.2 g. (0.2 mole) of sodium acetate in 250 ml. of ethanol and 75 ml. of water was heated at 70° overnight. The solvent was removed under reduced pressure and the residue was mixed with water and extracted with chloroform. The chloroform solution was dried (sodium sulfate) and concentrated under reduced pressure to give 20.4 g. (99%) of a 50/50 mixture of **1a** and **1b** as a brown oil which crystallized on standing, m.p. 90-92°; nmr (DMSO-d_6): δ 0.40-0.70 (m, 2H, cyclopropylmethylene of **1a**), 0.80-1.0 (m, 2H, cyclopropylmethylenes of **1b**), 1.21-1.60 (m, ½H, cyclopropylmethine of **1a**), 2.02-2.31 (m, ½H, cyclopropylmethine of **1b**), 3.35 (s, 1H, methylene of **1a**), 4.21 (s, 1H, methylene of **1b**), 6.95 (s, ½H, NOH of **1b**), 8.50-8.82 (m, 2H, pyrazine), 9.18 (s, 1H, pyrazine), 12.09 (s, ½H, NOH of **1a**).

Mixture of **4a** and **4b**.

This mixture was a brown solid, m.p. 161-163°; nmr (DMSO-d_6): δ 0.35-0.70 (m, 4H, cyclopropylmethylenes of **4a** + **4b**), 1.10-1.40 (m, ½H, cyclopropylmethine of **4a**), 1.50-1.90 (m, ½H, cyclopropylmethine of **4b**); 3.27 (d, 2H, methylene of **4a** + **4b**), 6.90 (s, ½H, NOH of **4b**), 7.31 (s, ½H, NOH of **4a**), 7.50-7.70 (m, 2H, pyridine), 8.50-8.70 (m, 2H, pyridine).

Mixture of **7a** and **7b**.

This mixture was a brown solid, m.p. 114-117°; nmr (DMSO-d_6): δ 0.40-0.70 (m, 2H, cyclopropylmethylene of **7a**), 0.70-0.95 (m, 2H, cyclopropylmethylene of **7b**), 1.10-1.40 (m, ½H, cyclopropylmethine of **7a**); 1.60-2.00 (m, ½H, cyclopropylmethine of **7b**), 3.02 (d, J = 18 Hz, 1H, methylene of **7a**), 3.30 (d, J = 18 Hz, 1H, methylene of **7b**), 6.78 (s, ½H, NOH of **7b**), 7.34 (s, ½H, NOH of **7a**), 7.40-7.60 (m, 1H, pyridine), 7.80-8.10 (m, 1H, pyridine), 8.50-8.90 (m, 2H, pyridine).

Mixture of **10a** and **10b**.

This mixture was a brown oil; nmr (DMSO-d_6): 0.35-0.65 (m, 2, cyclopropylmethylene of **10a**), 0.75-1.10 (m, 2H, cyclopropylmethylene of **10b**), 1.1-1.5 (m, ½H, cyclopropylmethine of **10a**), 2.00-2.30 (m, ½H, cyclopropylmethine of **10b**), 3.30 (s, 1H, methylene of **10a**), 4.15 (s, 1H, methylene of **10b**), 7.15-7.50 (m, 1H, pyridine), 7.65-8.10 (m, 2H, pyridine), 8.23 (s, ½H, NOH of **10b**), 8.40-8.60 (m, 1H, pyridine), 11.45 (s, ½H, NOH of **10a**).

Table I

Physical Properties of Isoxazoles

Compound	4-Position Proton Nmr (DMSO-d_6) δ	M.p. °C	% Yield Hydrochloric Acid/Ethanol	% Yield Sulfuric Acid (b)
2	6.78	87-90	94	14
3	7.02	99-100	0	15
5	6.84	76-80	87 50/50 mixture	18
6	7.04	102-108		36
8	6.81	72-76	84 50/50 mixture	48
9	6.93	72-75		37
11	6.84	149-151 (a)	53	29
12	6.94	169-175 (a)	0	21
14	6.91	105-107	80	4
15	7.12	141-142	0	23
17	6.81	63-64	59	18
18	7.13	107-108	0	18

(a) Hydrochloride salt. (b) Represents isolated yield from isomer mixture.

Table II

Analytical Data

Formula	% Calcd. C	H	N	Cl	% Found C	H	N	Cl
2	64.16	4.85	22.45	--	64.47	4.97	22.48	--
3	64.16	4.85	22.45	--	64.05	4.98	22.30	--
5	70.95	5.41	15.05	--	70.95	5.41	15.05	--
6	70.95	5.41	15.05	--	71.20	5.55	14.88	--
8	70.95	5.41	15.05	--	70.85	5.59	15.07	--
9	70.95	5.41	15.05		70.86	5.62	14.74	
11	59.33	4.98	12.58	15.92	59.26	4.99	12.67	15.80
12	59.33	4.98	12.58	15.92	59.25	5.14	12.92	16.06
14	64.16	4.85	22.45	-	63.96	4.80	22.51	--
15	64.16	4.85	22.45	--	63.82	5.22	22.16	--
17	64.16	4.85	22.45	--	64.16	4.85	22.15	--
18	64.16	4.85	22.45	--	64.24	5.07	22.61	--
1a + 1b	58.53	5.40	20.48	--	58.43	5.37	20.65	--
4a + 4b	64.69	5.92	13.72	--	64.91	6.20	13.66	--
7a + 7b	64.69	5.92	13.72	--	64.85	6.17	13.72	--
10a + 10b	64.69	5.92	13.72	--	64.56	6.12	13.94	--
13a + 13b	58.53	5.40	20.48	--	58.10	5.30	20.30	--
16a + 16b	58.53	5.40	20.48	--	58.16	5.23	20.02	--

Mixture of **13a** and **13b**.

This mixture was a tan solid, m.p. 135-137°; nmr (DMOS-d_6): δ 0.40-0.65 (m, 2H, cyclopropylmethylene of **13a**), 0.80-1.00 (m, 2H, cyclopropylmethylene of **13b**), 1.20-1.60 (m, ½H, cyclopropylmethine of **13a**), 2.00-2.30 (m, ½H, cyclopropylmethine of **13b**), 3.42 (s, 1H, methylene of **13a**), 4.28 (s, 1H, methylene of **13b**), 6.94 (s, ½H, NOH of **13b**), 7.60-7.85 (m, 1H, pyridazine), 8.05-8.25 (m, 1H, pyridazine), 9.15-9.35 (m, 1H, pyridazine), 12.11 (s, ½H, NOH of **13a**).

Mixture of **16a** and **16b**.

This mixture was a brown oil; nmr (DMSO-d_6): 0.75-1.28 (m, 4H, cyclopropylmethylene of **16a** + **16b**), 1.75-2.00 (m, ½H, cyclopropylmethine of **16a**), 2.10-2.40 (m, ½H, cyclopropylmethine of **16b**), 2.86 (d, J = 18 Hz, 1H, methylene of **16a**), 3.60 (d, J = 18 Hz, 1H, methylene of **16b**), 7.73-8.00 (m, 1H, pyrimidine), 8.69-8.92 (m, 1H, pyrimidine), 9.08-9.32 (m, 1H, pyrimidine), 10.10 (s, ½H, NOH of **16b**), 12.30 (s, ½H, NOH of **16a**).

Acknowledgments.

Analyses were performed by Mr. L. Brancone and staff; nmr spectra by Mr. G. Morton, and mass spectra by Dr. R. Hargreaves.

REFERENCES AND NOTES

(1) R. A. Barnes, "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N.Y., 1957, Chapter 7.

(2) A. Quilico, "The Chemistry of Heterocyclic Compounds. Five and Six-membered Compounds with N and O", A. Weissberger, Ed., Interscience, New York,N.Y., 1962, Chapter 1.

Table III

Mass Spectrum Data -- m/e (Relative Intensity)

Formula						
2	187 (63, M^+),	146 (18),	79 (60),	69 (100)		
3	187 (58, M^+),	108 (100),	107 (21),	79 (37)		
5	186 (57, M^+),	145 (45),	118 (77),	78 (48),	69 (100)	
6	186 (61, M^+),	108 (43),	106 (70),	80 (38),	78 (85)	
8	186 (58, M^+),	145 (41),	118 (25),	78 (50),	69 (100)	
9	186 (100, M^+),	108 (45),	106 (77),	80 (41),	78 (91)	
11	186 (100, M^+),	145 (44),	118 (27),	117 (13),	78 (95),	69 (82)
12	186 (92, M^+),	108 (66),	106 (25),	80 (58),	80 (58),	78 (100)
14	187 (100, M^+),	146 (22),	79 (25),	69 (83)		
15	187 (100, M^+),	108 (46),	79 (79)			
17	187 (100, M^+),	146 (20),	79 (68),	69 (93)		
18	187 (53, M^+),	108 (100),	79 (62),			
(1a + 1b)	205 (12, M^+),	122 (12),	107 (9),	84 (7),	69 (100)	
(4a + 4b)	204 (10, M^+),	136 (72),	121 (4),	106 (6),	84 (4),	69 (100)
(7a + 7b)	204 (9, M^+),	121 (7),	106 (8),	84 (4),	69 (100)	
(10a + 10b)	204 (12, M^+),	186 (8),	121 (8),	106 (6),	84 (5),	69 (100)
(13a + 13b)	205 (13, M^+),	187 (88),	137 (35),	122 (10),	84 (10),	69 (100)

(3) N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.*, **2**, 365 (1963).

(4) The percentage of each oxime in a mixture was determined by pmr analysis.

(5) Position isomers were readily assigned on the basis of the mass spectrum fragment arising from the loss of the substituent at the 5 position of the isoxazole ring as a radical. See C. F. Beam, M. C. Dyer, R. A. Schwarz, and C. R. Hauser, *J. Org. Chem.*, **35**, 1806 (1970). It was observed that the pmr signal of the 4-isoxazolyl proton of the 5-cyclopropyl isomer had a higher field position that the corresponding 3-cyclopropyl isomer in each case. (See Table I).

(6) All attempts to separate these oxime mixtures by a variety of chromatographic techniques were unsuccessful.

(7) Oximes **1a**, **10a**, **13a** and **16a** are drawn syn to the heterocyclic ring on the basis of the low pmr field position of their oxime proton.

(8) Melting points were determined in a Hershberg apparatus and are uncorrected. Nmr spectra were determined on a Varian HA-100 instrument using tetramethylsilane as an internal standard. Mass spectra were run on an AEI MS-9 spectrometer at 70 eV. Partition chromatographs were run on Celite 545 using heptane-acetonitrile for the partition system.