SYNTHESIS OF IMIDAZO[4,5-d]IMIDAZOLE-2,5-DITHIONES BY CRISSCROSS ADDITION REACTION OF 1,4-DIAZA-1,3-DIENES TO ISOTHIOCYANATOTRIMETHYLSILANE

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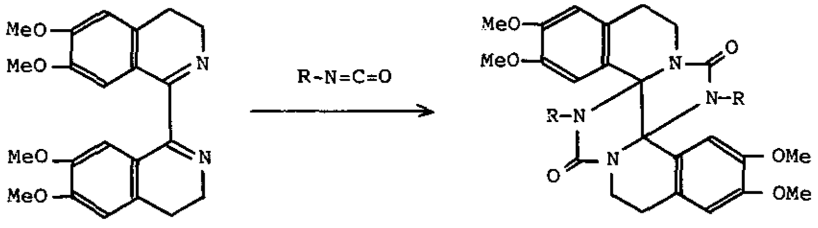
Abstract——*Treatment* of 1,4-disubstituted 1,4-diaza-1,3-dienes with isothiocyanatotrimethylsilane yielded crisscross adddition products, 1,4-disubstituted tetrahydroimidazo[4,5-d]imidazole-2,5-dithiones.

Cycloaddition reactions of heterodienes have now become one of the most useful synthetic methods for heterocycles.[1] Among these heterodienes it has been known that 1,4-diaza-1,3-dienes (α-diimines) behave as dienes or dienophiles in hetero Diels-Alder reactions and also participate in [2+2] cycloadditions.[2] However, [2+3] crisscross addition reactions, which have been well-known in the reactions of 2,3-diaza-1,3-dienes (azines) with heterocumulenes or alkenes,[3] have been scarecely studied so far, and only limited examples were reported by Sakamoto et al.;[4] 1,1'-biisoquinolines (1) reacted with aryl and benzoyl



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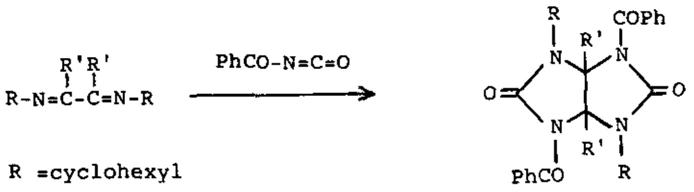
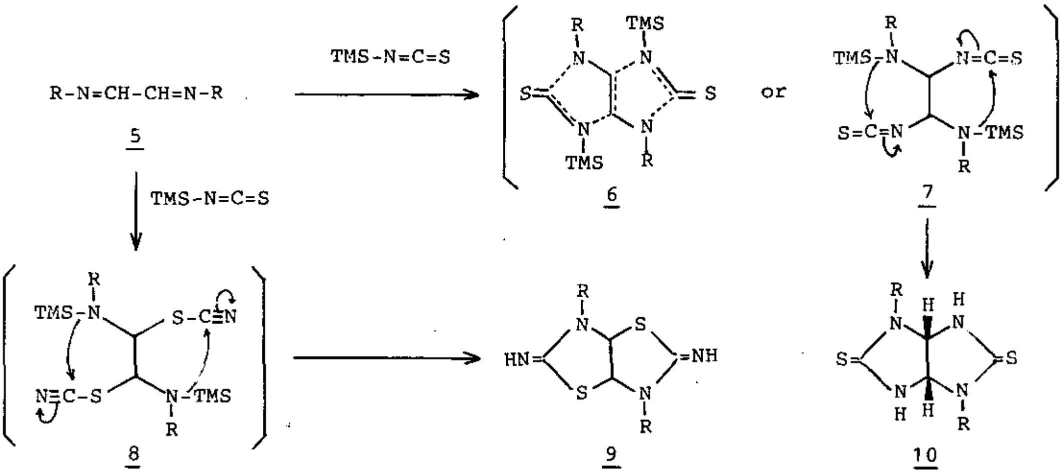


3 R =cyclohexyl
R'=H, Me

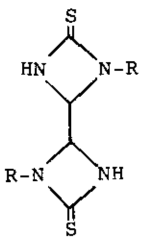
4

isocyanates to give crisscross adducts 2. However, simpler diazadienes (3) could yield the adduct 4 only when treated with benzoyl isocyanate in refluxing toluene. In connection with our interest in synthesis of heterocycles using silicon pseudohalides[5] we have found that simple 1,4-diaza-1,3-dienes (5) reacted easily with isothiocyanatotrimethylsilane (Me_3Si-N=C=S, TMS-NCS) to give crisscross adducts 10.

Treatment of 5a with TMS-NCS in tetrahydrofuran at room temperature gave a 1:2 adduct, whose structure was assigned as follows to be imidazo[4,5-d]imidazole (10a). The ir spectrum of the product showed the presence of amino groups, while the ^{1}H-nmr and ^{13}C-nmr spectra indicated a signal of one singlet methine proton at δ 6.03 ppm and that of one doublet methine carbon at δ 75.49 ppm, respectively, suggesting that the structure is symmetrical. Three structures 9a, 10a, and 11a seem possible on the basis of the above data and the mechanistic consideration. Nucleophilic addition of isothiocyanato anion to the imine bonds of 5a would form the intermediate 7a, which cyclizes to give the crisscross adduct 10a. Concerted [2+3] addition of TMS-NCS to 5a would also produce 10a. On the other hand, attack of sulfur atom of TMS-NCS to 5a because of its ambident character[6] would form the intermediate 8a, which cyclizes to give the isomeric 1,3-thiazolo[5,4-d]-1,3-thiazole (9a).



5-11	R
a	p-EtOC$_6$H$_4$
b	p-MeOC$_6$H$_4$
c	p-MeC$_6$H$_4$
d	Me$_2$CH
e	cyclohexyl
f	n-C$_4$H$_9$



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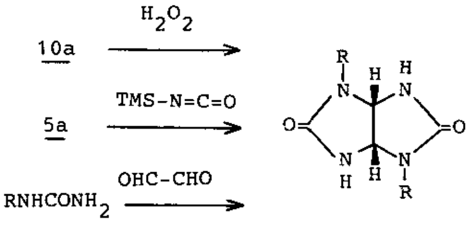

R=p-EtOC$_6$H$_4$

12

Table 1. 1,4-Disubstituted tetrahydroimidazo[4,5-d]imidazole-2,5-dithiones (10)

10	Reaction conditions			Yield	mp/°C	Molecular	Found (Calcd)		
	Solvent	Temp.	Time/h	%	(Solvent)	formula	C %	H %	N %
a	THF	rt	3	29	>300	$C_{20}H_{22}N_4O_2S_2$	57.76	5.44	13.39
					(THF)	(414.55)	(57.95	5.35	13.52)
b	dioxane	rt	3	24	291-293	$C_{18}H_{18}N_4O_2S_2$	55.66	4.59	14.45
					(DMF)	(386.50)	(55.94	4.69	14.50)
c	dioxane	rt	3	26	289-291	$C_{18}H_{18}N_4S_2$	60.71	5.15	15.74
					(THF)	(354.50)	(60.99	5.12	15.80)
d	dioxane	rt	1	57	293-294	$C_{10}H_{18}N_4S_2$	46.18	6.89	21.72
					(THF)	(258.41)	(46.48	7.02	21.68)
e	THF	rt	1	53	>300	$C_{16}H_{26}N_4S_2$	57.25	7.71	16.52
					(THF)	(338.54)	(56.77	7.74	16.55)
f	THF	rt	3	12	270-272	$C_{12}H_{22}N_4S_2$	50.00	7.68	19.66
					($CHCl_3$)	(286.47)	(50.31	7.74	19.56)

As [2+2] cycloaddition of the imine bonds of 5 to ketene has been reported,[7] 2,2'-bidiazetidine-4,4'-dithione (11a) is also compatible with the spectral data. In order to distinguish among these structures 9a, 10a, and 11a, oxidation of thione to ketone by hydrogen peroxide was undertaken. The oxidation product showed the carbonyl absorptions at 1730 and 1680 cm^{-1} in the ir spectrum, excluding the structure 9a and preferring imidazo[4,5-d]imidazole-2,5-dione (12) to 2,2'-bidiazetidine-4,4'-dione[8] derived from 11a. Imidazo[4,5-d]imidazole-2,5-diones have been synthesized from 1,2-dicarbonyl compounds and ureas,[9] and less strained cis-configuration has been established by measurement of the dipole moment.[10] 1,4-Bis(p-ethoxyphenyl)-cis-tetrahydroimidazo[4,5-d]imidazole-2,5-dione (12) prepared independently[10] from glyoxal and N-(p-ethoxyphenyl)urea was identical with the oxidation product of 10a. Thus, the structure of the 1:2 adduct of 5a to TMS-NCS has been proved to be *1,4-bis(p-ethoxyphenyl)-cis-tetrahydroimidazo[4,5-d]imidazole-2,5-dithione* (10a). Other 1,4-diaza-1,3-butadienes (5b-f) were similarly treated with TMS-NCS in tetrahydrofuran or dioxane at room temperature, and the physical and spectral data are summarized in Tables 1 and 2. The oxidation product of 10e by hydrogen peroxide was also identical with the hydrolysis product of 4 (R'=H), 1,4-dicyclohexyltetrahydroimidazo[4,5-d]imidazole-2,5-dione.[4] Since methyl and phenyl isothiocyanates failed to react with 5a and were recovered

Table 2. Spectral data of 10

10	Ms/ m/z, M^+	Ir/ KBr, cm^{-1}	^1H-Nmr/ δ ppm, in DMSO-d_6
a	414	3180 1510 1465 1440 1295 1245	1.34 (t, J=7 Hz, 3H), 4.03 (q, J=7 Hz, 2H), 6.03 (s, 1H), 6.92 (d, J=9 Hz, 2H), 7.29 (d, J=9 Hz, 2H), 9.65 (s, 1H)
b	386	3180 1515 1490 1465 1440 1250	3.80 (s, 3H), 6.09 (s, 1H), 6.98 (d, J=8 Hz, 2H), 7.32 (d, J=8 Hz, 2H), 9.68 (s, 1H)
c	354	3160 1510 1495 1465 1440 1275	2.32 (s, 3H), 6.13 (s, 1H), 7.26 (s, 4H), 9.72 (s, 1H)
d	258	3150 2960 1490 1460 1240 1065	1.22 (d, J=7 Hz, 6H), 4.32-4.78 (m, 1H), 5.64 (s, 1H), 9.18 (s, 1H)
e	338	3190 2950 1505 1465 1265 1240	1.68 (br s, 10H), 4.13 (br s, 1H), 5.64 (s, 1H), 9.20 (s, 1H)
f	286	3170 2960 1485 1250 1220 1070	0.89-1.64 (m, 7H), 3.00-3.80 (m, 2H), 5.59 (s, 1H), 9.32 (s, 1H)

unchanged, it appears that the present reaction would be a stepwise process through the intermediate 7 rather than the concerted transition state 6.
Isocyanatotrimethylsilane ($Me_3Si-N=C=O$) was also allowed to react with 5a-f. However, only 12 was obtained from 5a in 14% yield.

EXPERIMENTAL

Melting points were determined by using a Yanako micromelting point apparatus. Ir spectra were obtained on a JASCO A-102 spectrophotometer. Mass and ^1H-nmr spectra were determined on a JEOL JMS-DX 300 spectrometer and JEOL JMN-PMX 60 spectrometer, respectively. Microanalyses were carried out with a Yanako CHN CODER MT-5. Measurement of ^{13}C-nmr spectra was performed at Dai-ichi Seiyaku Co., Ltd.. The starting materials 5b-f[11] and TMS-NCS[12] were prepared according to the literatures. The compound 5a, mp 166-168°C, was prepared similarly to 5b.

1,4-Bis(p-ethoxyphenyl)-cis-tetrahydroimidazo[4,5-d]imidazole-2,5-dithione (10a). To a stirred solution of 5a (296 mg, 1.0 mmol) in THF (9 ml) TMS-NCS (525 mg, 4.0 mmol) was added. The yellow reaction mixture turned dark red immediately. After stirring for 3 h at room temperature the solvent was evaporated. MeOH (5 ml) was added to the residue and the mixture was allowed to stand for 10 h to cause precipitation. Collection of the precipitates followed by recrystallization from THF afforded 10a (119 mg, 29%). ^{13}C-Nmr (DMSO-d_6): δ 14.59 (q), 63.19 (t), 75.49 (d), 114.37 (d), 128.89 (d), 130.09 (s), 157.43 (s), 181.56 (s).

In the cases of 10b, c, d, and e the precipitates formed after stirring were collected and recrystallized. The product 10f was obtained by washing the evaporated residue with ether followed by recrystallization.

1,4-Bis(p-ethoxyphenyl)-cis-tetrahydroimidazo[4,5-d]imidazole-2,5-dione (12).

From N-(p-ethoxyphenyl)urea. The product 12 (149 mg, 13%) was prepared according to the literature method[10] by refluxing a mixture of N-(p-ethoxyphenyl)urea (360 mg, 2.0 mmol) and gyoxal trimeric dihydrate (70 mg, 1.0 mmol) in a mixed solvent (MeOH 5 ml and water 5 ml) in the presence of several drops of concentrated hydrochloric acid for 6 h. mp >300 °C (DMF). Ir (KBr): 3200, 1730, 1685, 1515, 1475, 1270 cm^{-1}. ^{1}H-Nmr (CF_3COOH): δ 1.53 (t, J=7 Hz, 3H), 4.31 (q, J=7 Hz, 2H), 6.13 (s, 1H), 7.13 (d, J=9 Hz, 2H), 7.39 (d, J=9 Hz, 2H). Ms: m/z 382 (M^+). Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.80; N, 14.65. Found: C, 62.76 ; H, 5.96; N, 14.69.

From 10a. To a solution of 10a (208 mg, 0.50 mmol) in acetone (5 ml) 30% aqueous hydrogen peroxide (1.1 g, 10 mmol) was added dropwise and the mixture was refluxed for 5 h. Collection of the precipitates followed by washing with MeOH gave 12 (11 mg, 6%).

From 5a. A mixture of 5a (296 mg, 1.0 mmol) and isocyanatotrimethylsilane (416 mg, 4.0 mmol) in dry THF (4 ml) was refluxed for 10 h under nitrogen atomosphere. After evaporation of the solvent MeOH (5 ml) was added to the residue and collection of the precipitates followed by washing with MeOH gave 12 (54 mg, 14%).

Oxidation of 10e. To a stirred solution of 10e (169 mg, 0.50 mmol) in acetone (15 ml) aqueous 30% hydrogen peroxide (600 mg, 5.3 mmol) was added dropwise. After refluxing for 3 h the precipitates were collected and washed with MeOH to give 1,4-dicyclohexyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (115 mg, 75%), mp >300°C (DMF) (lit.[4] mp >300°C). Ms: m/z 306 (M^+). Ir (KBr): 3220, 2950, 1690, 1490 cm^{-1}.

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