Title	Thermal rearrangement of 2-(N-alkylthiocarbamoyl) or 2-(N-arylthiocarbamoyl) alkylamino-4-alkylthiazole
Sub Title	
Author	山本, 有一(Yamamoto, Yuichi) 与田, 玲子(Yoda, Reiko) 小口, 敬子(Koguchi, Keiko) 高橋, 智子(Takahashi, Tomoko) 本村, 直子(Motomura, Naoko)
Publisher	共立薬科大学
Publication year	1981
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.26 (1981.) ,p.25- 35
JaLC DOI	
Abstract	
Notes	原報
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000026- 0025

慶應義塾大学学術情報リポジトリ(KOARA)に掲載されているコンテンツの著作権は、それぞれの著作者、学会または出版社/発行者に帰属し、その権利は著作権法によって 保護されています。引用にあたっては、著作権法を遵守してご利用ください。

The copyrights of content available on the KeiO Associated Repository of Academic resources (KOARA) belong to the respective authors, academic societies, or publishers/issuers, and these rights are protected by the Japanese Copyright Act. When quoting the content, please follow the Japanese copyright act.

共立薬科大学 Annu. Rep. Kyoritsu Coll, Pharm.

Thermal Rearrangement of 2–(N–Alkylthiocarbamoyl) or 2–(N–Arylthiocarbamoyl)alkylamino–4–alkylthiazole

Yuichi YAMAMOTO, Reiko Yoda, Keiko Koguchi, Tomoko Takahashi, and Naoko Motomura

山本 有一,与田 玲子,小口 敬子,高橋 智子,本村 直子

Effect of a substituent, solvent, reaction temperature, and presence or absence of a base on the thermal rearrangement of 2-[N-alkyl(or aryl)thiocarbamoyl]alkyl(or aryl)amino-4-alkyl(or aryl)thiazole was examined. The presence of an alkyl group in the amino group at 2-position and that of an alkyl (or phenyl) group in the 4-position of the thiazole ring were found to be essential for the rearrangement of the thiocarbamoyl group. The presence of a pyridine base markedly enhanced the reaction rate of the thermal rearrangement but was not specific to this reaction. On the other hand, several kinds of carbamoyl derivatives showed there was no rearrangement of the carbamoyl group.

We have already reported¹⁾ that thermal reaction of 4-methyl-2-methylaminothiazole and methyl isothiocyanate in toluene in the presence of pyridine afforded 4-methyl-2-(N-methylthiocarbamoyl)methylaminothiazole 2f and 4-methyl-2-methylamino-5-(N-methylthiocarbamoyl)thiazole 3f, while refluxing of 2f in pyridine resulted in its thermal rearrangement to 3f, and that the solvent pyridine played an important role in this thermal rearrangement reaction.



In the present series of work, we examined the effect of substituents, R,R', and R'' in the general formula, 2-(N-alkylthiocarbamoyl) or 2-(N-arylthiocarbamoyl)alkylamino-4-alkylthiazole 2, on the thermal rearrangement, and the effect of the solvent, base, and reaction temperature on the rearrangement reaction was also examined.

First, in order to examine the effect of a substituent on the thermal rearrangement of 2 to 3, 2 was refluxed in pyridine and the presence or absence of the rearrangement reaction was examined by thin-layer chromatography (TLC). Its result is summarized in Table 1. It was found that 2a, b, c (R=H) did not undergo the rearrangement reaction and that,

¹⁾ Y. Yamamoto, R. Yoda, and C. Tamura, Chemistry Letters, 1147-1148 (1975).

		HR	2	
compd. No.	R	R′	R ″	Rearrangement
2 a	Н	CH3	CH3	
2 b	н	$\langle \overline{0} \rangle$	CH3	—
2 c	Н	CH ₃	Н	
2 d	CH3	CH_3	Н	
2 e	CH3	$\langle \overline{0} \rangle$	Н	-
2 f	CH3	CH ₃	CH3	+
2 g	CH3	C_2H_5	CH3	+
2 h	CH3	\bigcirc -CH ₂ -	CH3	+
2 i	CH3	$\overline{\langle 0 \rangle}$	CH3	+
2 ј	CH3	Cl-(0)-	CH	+
2 k	CH3	O_2N-	CH ₃	-+
2 1	CH3	CH ₃	$\langle 0 \rangle$	<u> </u>
2 m	CH3	$\langle 0 \rangle$	$\langle 0 \rangle$	+
2 n	$\langle \overline{0} \rangle$	CH3	CH ₃	*

Table 1. The effect of substituents for the thermal rearrangement (R, R' and R")

 $\overset{S}{\mathbf{R'-N-C-N-N}} \overset{N}{\underset{S}{\overset{H}{\longrightarrow}}} \overset{R''}{\underset{S}{\overset{H}{\longrightarrow}}}$

decomposition before rearrangement

even when R is methyl, the rearrangement reaction did not take place when there was no electron-donating group like methyl in the 4-position (R") of the thiazole ring, *i.e.*, 2c, d, e, with R"=H. In other words, when R or R" is H, the rearrangement does not take place, irrespective of the kind of a substituent at R'. The rearrangement does take place when R=R"=methyl, *i.e.*, 2f to 2k. In this case, the rearrangement occurs faster when R' is an aromatic group than when it is an aliphatic group, and relatively faster when the aliphatic group is smaller in molecular weight, such as the methyl group. The rearrangement tended to occur more easily in the order of aralkyl, alkyl, and aryl group. With R=methyl and R"=phenyl 2l, m, as in the case of R"=methyl, the rearrangement reaction occurs faster when R' is phenyl than when it is methyl (2m \geq 2l).

In order to examine the difference, if any, in the rate of rearrangement between methyl and phenyl groups in \mathbb{R}'' , when \mathbb{R} is methyl, the reaction was compared with 2f, 2i, 2l, and 2m. The time required for the rearrangement product 3 to be formed was found to be 5 min for 2i, 10 min for 2m, 4 hr for 2f, and 5—6 hr for 2l. These results indicated that the rearrangement occurred faster when \mathbb{R}' is phenyl than when it is methyl, irrespec-

tive of whether R" is methyl or phenyl.

Comparison of R=methyl 2f and R=phenyl 2n, when R'=R''=methyl showed that heating of 2n (R=phenyl) in pyridine resulted merely in its decomposition into 4-methyl-2-phenylaminothiazole and methyl thiocyanate, and the rearrangement product 3n was not formed even on heating for 12 days.

Next, the reaction of 2b and 2e, whose rearrangement reaction was negative from TLC follow-up, was examined by ultraviolet (UV) spectra. Heating of 2b or 2e (2.9 mM concentration) in pyridine, at a bath temperature of 142°C, resulted in the disappearance of 2b and 2e absorptions already 15 min after the start of heating, and the absorption at 300 nm increased with time. Measurement of infrared (IR) absorption spectra (KBr sandwich method) of the reaction solution showed the presence of a specific absorption of ν N=C=S at 2080 cm⁻¹ about 15 min after the start of heating in both compounds. These spectral evidence indicate that 2b and 2e undergo only the decomposition reaction and do not form the 5-thiocarbamoyl compound 3.

The same UV and IR spectral examinations were made with the reaction of 2i and 2k respectively, which undergo a very fast rearrangement reaction. First, the effect of a substituent at R' was examined at a constant temperature (68°C), constant concentration (1 mM), and with pyridine as a solvent. As shown in Fig. 1, decreasing rate of absorbance



Fig. 1. The effect of substituents (R'=Phenyl, p-Nitrophenyl) in pyridine at $68 \pm 0.1^{\circ}$.

-27 -

No. 26 (1981)

of 2, *i.e.*, disappearance rate of 2, was greater when $\mathbf{R'}$ =phenyl 2i than when it was p-nitrophenyl 2k. In both 2i and 2k, the specific absorbance for v N=C-S appeared at 2080 cm⁻¹ in their IR spectra 10 min after the start of the reaction, showing decomposition of 2, indicating that the disappearance rate of 2 equals decomposition rate of 2. The specific absorption of v N=C=S in IR spectrum of 2i did not disappear even after heating for 8 hr, and the absorption at 366 nm 3i did not appear in its UV spectrum. In the case of 2k, absorption of v N=C=S disappeared after heating for 5 hr, absorption of 3k began to appear at 381 nm after 30 min of heating. Decomposition reaction of 2 seemed to be greater in 2i than in 2k but the rearrangement reaction was found to be faster in 2k.

Effect of the solvent on the rearrangement reaction of 2i and 2k respectively, was examined at a constant reaction temperature (68°C) and constant concentration (10⁻² mM), using pyridine, cyclohexane, or toluene as a solvent. In the same solvent, decomposition reaction of 2i was faster than that of 2k. The decomposition became slower in the order of pyridine, cyclohexane, and toluene in both 2i and 2k. When cyclohexane or toluene was used as a solvent, the rearrangement product 3 was not formed even 8 hr after the start of heating. By the use of pyridine as a solvent, only 3k ($\mathbf{R'}=p$ -nitrophenyl) was began to be formed after 46 min, and the rearrangement was completed after 17 hr. Decomposition of 2 seems to take place irrespective of the solvent but its rearrangement to 3 seems to require the presence of pyridine.

Effect of reaction temperature on the rearrangement reaction was then examined at a constant concentration (1 mM), using pyridine as a solvent, with a reaction temperature of 68°C and 142°C. As shown in Table 2, absorption of 2i at 340 nm disappeared faster when reacted at 142°C, this being more than 12-fold of the rate at 68°C, although the absorption for the rearrangement product 3i at 366 nm was not detected. In the case of 2k, disappearance of the absorption at 322 nm and appearance of the absorption of the rearrangement product 3k at 381 nm were faster at 142°C, being 13-fold of those at 68°C. These results indicate the marked dependence of the rearrangement reaction on the reaction temperature.

compd.	2i R'=	= < 0 >	2 k R'=-	
temp.	340 nm disappearance	366 nm appearance	322 disappearance	381 appearance
68±0.1°	180 min (every 10 min)		180 min	40 min
$142 \pm 0.5^{\circ}$	15 (every 2 min)		13	3

Table 2. The effects of reaction temperature in pyridine(detected by UV Absorption in pyridine)

Since the foregoing experimental results seemed to indicate that pyridine was indispensable for this rearrangement reaction, examinations were made to see whether pyridine worked specifically for this reaction or whether it worked as a base. First, solvents with different basicity were selected; pyridine $(pK_a 5.17)$, quinoline $(pK_a 4.80)$, and triethylamine $(pK_a 10.67)$. Difference in the reactivity was examined by using one of these as a solvent or a catalyst (equimolar amount with 2). With 2k at a concentration of 10 mM and reaction temperature of 68°C, the rearrangement reaction was followed by TLC. When the above solvents were used as a basic solvent, decomposition rate of 2k was constant, irrespective of pK_a but the formation rate of the rearrangement product 3k was the fastest with pyridine, and the rate decreased in the order of the size of pK_a (triethylamine, quinoline). TLC result suggested that *p*-nitrophenyl isothiocyanate formed by thermal decomposition of 2k was further decomposed in any of these solvents to form *p*-nitroaniline 6 which was obtained in a crystalline form when pyridine was used.

Then the reaction was carried out in toluene, which was the most difficult solvent to cause the rearrangement reaction, and the three kinds of foregoing bases was used as a catalyst. This resulted in shorter time for decomposition of $2\mathbf{k}$ and the rearrangement product $3\mathbf{k}$ appeared after 4-4.5 hr while the appearance of the decomposition by-product **6** became slower. This was the same for all three kinds of bases.

As shown in Table 3, rearrangement reaction of 2 to 3 is not characteristic to pyridine but is a general reaction in the presence of a base, although the rearrangement was most facilitated by the use of pyridine. The use of triethylamine as a solvent resulted in greater formation of the by-product, while the reaction carried out in toluene, with the use of triethylamine as a catalyst, facilitated the formation of the rearrangement product 3, with least formation of 6.

We had thus been examining the rearrangement reaction of thiocarbamoyl derivatives and further examined this reaction, if any, in carbamoyl derivatives.

	appearance tim	e (detect	ed by TLC)
solvent		0	
	H	3 k	6
pyridine	4 min	10	8
quinoline	4	70	270
triethylamine	4	50	155
catalyst/toluene			
pyridine/ "	9	260	165
quinoline/ "	5	260	330
triethylamine/ "	7	240	1350

Table 3. Thermal rearrangement (at 68°C) of 2k to 3k in basic solvents and toluene solvent in the presence of basic catalysts.



For this experiment, compounds similar to thiocarbamoyl derivatives that underwent relatively facile rearrangement reaction were selected; compounds with R=R''=methyl, and with R'=methyl 2'f, R'=phenyl 2'i, and R'=p-nitrophenyl 2'k. The reaction was carried out by refluxing in pyridine at their concentration of 10 mM, and the reaction was followed by TLC. Decomposition rate of 2' decreased in the order of 2'k, 2'i, and 2'f, and the rearrangement product 3' was obtained only from 3'i (R'=phenyl). Heating of 2'f resulted in its gradual decomposition and 3' was not formed even after heating for 8—9 days. After heating of 2'k, 1 immediately, N,N'-bis(p-nitrophenyl)urea 5, and 6 were detected by TLC. 5 and 6 were considered to have been formed from p-nitrophenyl isocyanate, produced by the decomposition of 2'k, in the presence of a minute amount of water. This p-nitrophenyl isocyanate is thought to react with water before undergoing above the rearrangement reaction.

Difference in the rearrangement reaction between thiocarbamoyl and carbamoyl derivatives is assumed to be due to the difference in the reactivity of alkyl or aryl isothiocyanate and alkyl or aryl isocyanate respectively formed by the decomposition of 2 and 2'.

Physical properties and analytical data are summarized in Table 4-7.

compd. (No.)	m.p. °C (recrys.)	$ \begin{matrix} \text{UV} \\ \lambda_{\text{max}}^{2\text{-ProH}} \\ \text{nm } \epsilon(\times 100) \end{matrix} $	NMR δ [*] _{c-H} ppm (solvent**)	Analysis Found (Calcd.)% C : H : N	MS M+ (R.I. %)	(m/e) fragment peak M ⁺ - RNCS
2 a	245 (dioxane)	255 102 292 231	6.72 (D)	38.57 4.65 22.89 (38.48 4.84 22.44)	187 (95)	114 (base)
2 b	169 (EtOH)	299 168 341 61	6.45 (C)		249(41)	114 (base)
2 c	170 (EtOH-H ₂ O)	255 104 289 204	7.02 (D)	35.11 3.63 24.23 (34.66 4.07 24.26)	173(76)	100 (base)
2 d	67 (EtOH-H ₂ O)	254 65 288 207	7.00 (C)	38.845.1022.18(38.484.8422.44)	187 (88)	114 (base)
2 e	98 (EtOH)	220 (sh) 296 262	7.20~7.64 (D)	52.92 4.36 16.74 (52.98 4.45 16.85)	249(43)	114 (base)
2 f	49 (EtOH)	257 (sh) 291 220	6.52 (C)	41.55 5.44 20.82 (41.76 5.51 20.87)	201 (22)	128 (base)
2 g	90 (EtOH-H ₂ O)	260 76 293 202	6.87 (D)	44.72 6.13 19.12 (44.62 6.09 19.20)	215 (59)	128 (base)
2 h	86 (EtOH)	261 91 293 198	6.92 (D)	56.555.2615.02(56.285.4515.15)	277 (53)	128 (base)
2 i	90 (EtOH)	244 85 345 172	6.89 (D)	54.79 4.84 15.89 (54.72 4.97 15.95)	263(8)	128(61)
2 ј	106 (EtOH)	233 94 306 221		48.62 3.92 14.07 (48.40 4.06 14.11)	297 (22)	128 (base)
2 k	148 (EtOH)	240 (sh) 319 213	6.57 (C)	46. 47 3. 74 18. 16 (46. 74 3. 92 18. 17)	308(6.2)	181(41)
2 1	116 (EtOH)	242 146 268 218 280 (sh) 300 (sh)	7.40~7.88 (D)	54.44 4.89 15.96 (54.72 4.98 15.95)	263 (24)	190 (base)
2 m	128 (EtOH)	250 139 282 194 304 195	7.01~7.65 (C)	63.45 4.87 13.06 (62.74 4.65 12.91)	325 (2)	190 (93.2)
2 n	146 (ligroin)	258 72 292 200	6.42 (C)	54.62 4.94 15.98 (54.72 4.98 15.95)	263 (12)	190 (base)

Table 4. Physical properties and analytical data of 2a-n

* Chemical shift of the ring at position 5.

** (C): $CDCl_3$, (D): DMSO- d_6 .

					Н	$\begin{array}{c} N \xrightarrow{K'} H \\ -N \xrightarrow{K'} S \xrightarrow{H} C \\ CH_3 \\ CH_3 \\ \end{array}$			
compd.				UV X2-ProH X2-max		NMR solvent : DMSO-d ₆	Analysis Found (Calcd.) %	WS	(m/e)
(No.)	R	R'	m.p. °C (recrys.)	nm $\epsilon(imes 1$	(00)	δ −N <ch₃< th=""><th>С : Н : Л</th><th>M+ (R.I. %)</th><th>fragment peak M⁺ – SH</th></ch₃<>	С : Н : Л	M+ (R.I. %)	fragment peak M ⁺ – SH
3 f	CH ₃	CH3	249 (EtOH)	294 340	63 115	(d, 3H, $J = 4.5$ Hz)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	201(base)	168 (83)
90 ന	C ₂ H5	CH3	214 (EtOH)	233 291 344	57 60 60	2.78 (d, 3H, $J = 4.0$ Hz)	44.33 5.80 19.20 (44.62 6.09 19.20)		
3 h	O-CH ₁ -	CH3	186 (EtOH- H ₂ O)	256 280 348	110 93 57			277 (6)	246(5.8)
31	\bigcirc	CH3	213 (EtOH)	238 361	124 162	(d, 3H, $J = 4.9$ Hz)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	263(38)	230(38)
3 j	cl-<0>-	СН₃	271 (EtOH)	240 368	65 82		$\begin{array}{rrrr} 48.40 & 4.06 & 14.11 \\ (47.91 & 4.58 & 13.58) \end{array}$	297 (30)	264(16)
3 k	O ₂ N- <o>-</o>	CH3	245 (toluene)	250 381	sh 219	(d, 3H, $J = 4.0$ Hz)	46.57 3.56 17.81 (46.74 3.92 18.17)	308 (26)	275(23)
31	CH ₃		224 (EtOH)	246 353	207 99	(d, 3H) 2.97	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	263 (base)	230(16)
3 m	\bigcirc	\bigcirc	270 (EtOH)	235 373	178 133	(d, 3H, $J = 5.0 \text{ Hz}$)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	325 (45)	292 (23)

Table 5. Physical properties, and analytical data of **3f-m**

No. 26 (1981)

Table 6. Physical properties and analytical data of 2'f, 2'i and 2'k



compd.	R'	ш.р. °С		UV 12-Proh	NMR	Four	Analysis nd (Calco	(T) %		MS (m/e) fragment peak
(NO.)		(recrys.)	uu	$\epsilon(imes 100)$	δс-н ppm	 ບ	H	Z	M+ (R.I. %)	M+ -RNCS
2′ f	CH3	120 (EtOH)	265	103		45.06 (45.38	5.92 5.99	22. 41 22. 69)	185(11)	128 (base)
2' i	\bigcirc	54~5	240 275	96 191	6.42* (s, 1H)	58. 41 (58. 28	5.25 5.30	17.06 16.99)	247(13)	128 (base)
2′ k		$205 \sim 8$ (toluene)	264 323	84 197	6.89** (s, 1H)	49. 38 (49. 31	4.01 4.14	19.06 19.17)	292(7.4)	128 (base)
じ * 33	Dcl ₃ ** DMSO	9 p-								





0

ĊH₃

	MS (m/e)	fragment peak	M^+ (R.I. %) $M^{+-}N H^{-}$	247 (23) 155 (base)	
3′ i	Analysis	Found (Calcd.) %	C : H : N M	57.69 5.07 16.67	38. 28 5. 30 16. 99)
	NMR	solvent: DMSO-d ₆	δ −N <h<sup>13</h<sup>	2.86	(d, 3H, $J = 6.0 \text{ Hz}$) (5)
	UV	A ^{2-PrOH} A ^{max}	nm $\epsilon(\times 100)$	255 67	314 199
		ر ا ا	m.p. C (recrys.)	232	(EtOH)
			(No.)	: /6	-

No. 26 (1981)

No. 26 (1981)

Experimental

The following spectrometry was performed by applying the respective instrument. IR: Hitachi Infrared spectrophotometer EPI-G3, UV: Shimazu double beam spectrophotometer UV-200S, solvent: Propanol-2 für die Spektroskopie (MERK), MS: Nihon Denshi JMS-OSG (70 eV), NMR: Nihon Denshi JNM-NH-100 (100 MHz).

General procedure

2a, 2b

An equimolar amount of 2-amino-4-methylthiazole and methyl or phenyl isothiocyanate was heated on a steam bath for 1.5 hr. The crude product was recrystallized from ethanol solution.

2d

Methyl isothiocyanate (2.92 g, 0.04 mole) was added to a solution of 2-methylaminothiazole (4.8 g, 0.04 mole) in dry xylene (11 ml) and then pyridine (1.5 ml) as catalyst was added. After heating at 85° for 6 hr, the solvent was evaporated. The crude product was recrystallized from ethanol-water solution (40% yield, mp 67°).

2e

A solution of phenyl isothiocyanate (1.3 g, 0.02 mole) in dry toluene (4 ml) was added to a solution of 2-methylaminothiazole (2.3 g, 0.002 mole) in dry toluene (3 ml) and added pyridine (1.5 ml) as catalyst. After heating at 80° for 4 hr, the solvent was evaporated and then recrystallized from ethanol solution $(46\% \text{ yield}, \text{mp } 98^\circ)$.

2f, 2i, 2k

R' isothiocyanate (R'=methyl, phenyl, p-nitrophenyl) (0.025 mole) was dropwise added to a solution of 4-methyl-2-methylaminothiazole 1 (3.14 g, 0.0025 mole) in cyclohexane (20 ml) with stirring at room temperature. After heating at 50° for 4—6 hr, the solvent was evaporated. The crude product was treated with a solution of 2% HCl solution to remove unreacted substance 1. The crude product was collected and recrystallized from ethanol solution.

2g, 2h, 2j

R' isothiocyanate (R'=ethyl, benzyl, p-chlorophenyl) (0.01 mole) in dry toluene (2 ml) was added to a solution of 1 (1.3 g, 0.01 mole) in dry toluene (15 ml) and added pyridine (1.5 ml) as catalyst and then heated at 80° for 4—6 hr. After the removal of solvent, the crude product was recrystallized from ethanol or ethanol-water solution. **21**, **2m**, **2n**

21, 2m, 2n also were yielded by the same treatment as just above mentioned (In the case of 2n, 2m, cyclohexane was used as the solvent).

The rearrangement reaction of compound 2 to compound 3.

A solution of 2 (3 mM) in pyridine was heated at 140° with the reflux. After removal of the solvent from the reaction mixture under reduced pressure, the resulting residue

was treated with 2% solution to remove compound 1 which may partially be decomposed from 2. The undissolved part of crude products was recrystallized from the appropriate solvent shown in Table 5.

2'f, 2'i, 2'k

R' isocyanate (0.04 mole) in dry ether (50 ml) was dropwise added to a solution of 1 (5.1 g, 0.04 mole) in dry ether *(100 ml) at $3-5^{\circ}$ C for 1 hr with ice cooling. After stirring for 1-2 hr, the solvent was evaporated and then recrystallized or purified.

2'f: mp 121° (EtOH).

2'i: The crude product was chromatographied on silica gel (100 mesh up) to give 2'i from the mixture solvent of chloroform and benzene (1:2).

*2'k: In case of 2'k, toluene instead of ether was used as the solvent.3'i

A solution of 2'i (2.47 g, 0.01 mole) in dry pyridine (25 ml) was refluxed for 71 hr. Then the solvent was evaporated. After adding chloroform to the residue, the unsoluble substance was filtered off, and the filtrate was evaporated. The crude product obtained was recrystallized from ethanol solution to yield 3'i, mp 232°.