Intramolecular Photoreactions of Thiohomophthalimides with an Alkenyl Group in Their *N*-Side Chain. Regioselective Synthesis of Heterocycle-Fused Isoquinoline Derivatives Through [2+2] Photocycloaddition

Haruko Takechi*, Hajime Takahashi, and Minoru Machida

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

Received March 29, 2004

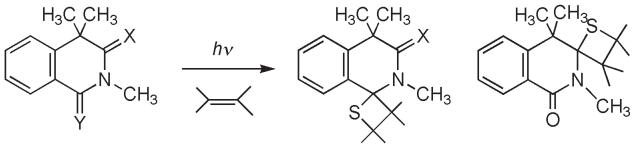
Upon irradiation, thiohomophthalimides with an alkenyl group in their *N*-side chain or at the benzylic position give tricyclic isoquinoline derivatives through regioselective intramolecular [2+2] cycloaddition or Norrish type II reaction, respectively, in good yields.

J. Heterocyclic Chem., **42**, 201 (2005).

During the course of our systematic studies on the photochemistry of nitrogen-thiocarbonyl systems, we found that aliphatic and aromatic thioimides (*e.g.*, thiophthalimide and thiosuccinimide) in each case undergo mainly [2+2] photocycloaddition (Paterno-Büchi reaction) with alkenes to give various thietanes and related compounds [1,2]. Studies on these photocycloadditions, however, are limited to five-membered thioimide systems except for certain six-membered aliphatic thioimide system [3]. To explore the application of cyclic thioimide photochemistry, we investigated the photoreactions of thiohomophthalimide systems (*e.g.*, 1,2,3,4-tetrahydro-1,3-dithioxoisoquinolines) having both an aromatic thiocarbonyl and an aliphatic thiocarbonyl in their framework. It was consequently found that the intermolecular thietane formation of thiohomophthalimide occurred regioselectively, in which the photocycloaddition of alkene occurred at the thiocarbonyl group in preference to the carbonyl group (Scheme 1) [4]. In the photoreactions of **1a** and **1b** having an aromatic thiocarbonyl group, addition of alkene occurred only at the aromatic thiocarbonyl group (1-position) to give thietanes (**2a** and **2b**) in good yields, respectively. In the case of **1c**, only the thietane compound was obtained, that is, an aliphatic thiocarbonyl group (3-position) showed high reactivity in comparison with the aromatic carbonyl group in their framework. As an application of this regioselective reaction, the construction of various ring-fused isoquinoline derivatives was examined through the intramolecular photocyclization of thiohomophthalimides with an alkenyl group in their *N*- side chain or at the benzylic position (4-position). The present report is concerned with the results of intramolecular cyclization reaction in these systems.

A series of dithiohomophtalimide derivatives (**4**,**5**, and **8**) were prepared from 1,2,3,4-tetrahydro-4,4-dimethyl-1,3-dithioxoisoquinoline (4,4-dimethyldithiohomophthalimide) and the appropriate alcohols, respectively. Monothiohomophthalimides (**11a** and **11b**) were obtained by the thionation of corresponding 4-alkenyl homophthalimides. The yields and analytical data of thiohomophthalimides **4**,**5**,**8**, and **11** are listed in Table 1.

Scheme 1



1a: X=S, Y=S
1b: X=O, Y=S
1c: X=S, Y=O

2a: X=S
2b: X=O

3c

Photolyses of substrates (**4**,**5**,**8**, and **11**) were performed in acetonitrile (5 mM) using a 500 kW high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere at room temperature. The results are shown in Scheme 2, Scheme 4, and Table 2.

In the photoreactions of a series of *N*-(3-butenyl)dithiohomophthalimides (**4a-c**), the [2+2] cycloaddition of an alkene moiety occurred regioselectively at the aromatic thiocarbonyl (1-position) in preference to the aliphatic thiocarbonyl (3-position), giving the corresponding ring-fused isoquinoline derivatives (**6a-c**) in 58-68% yields, respectively. Probably the ene-thiolactams **6** arise from the initially formed thietane through photochemical fission (cycloreversion) of the thietane ring [5]. The Process of dethioformation seems to be due to the strain of the thietane ring in fused ring system, and leads to a more stable conjugated system. Thus, the intramolecular reaction indicated regioselectivity similar to intermolecular reactions of dithiohomophthalimide as previously reported [4].

Similarly, photolyses of *N*-(4-pentenyl)dithiohomophthalimides (**5a-c**), having a longer *N*-alkenyl side chain than one of **4**, afforded the tricyclic six-membered ene-thiolactams (**7a-c**) in good yields (52-95%). These ring construction reactions can be reasonably explained in terms of a biradical intermediate [1,2], generated by addition of thiocarbonyl sulfur to the alkenyl moiety. Indeed it is supported by the fact that the yields of cyclized products (**6a-c**

Table 1

Physical Properties and Spectral Data for Thiohomophthalimides (**4,5,8** and **11**)

Compd.	Yield (%)	Appear-ance	Formula	HRMS Calcd (Found)	^{1}H-NMR(90 MHz, $CDCl_3$) δ
4a	65 [a]	Reddish oil	$C_{15}H_{17}NS_2$	275.0802 (275.0796)	1.72 (6H, s, CH_3x2), 2.3-2.7 (2H, m, NCH_2CH_2-), 4.9-5.3 (4H, m, NCH_2CH_2CH=CH_2), 5.5-6.0 (1H, m, CH=CH_2), 7.1-7.7 (3H, m, ArH), 8.3-8.5 (1H, m, ArH)
4b	45 [a]	Reddish oil	$C_{16}H_{19}NS_2$	289.0959 (289.0942)	1.73 (6H, s, CH_3x2), 1.83 (3H, br s, CH_3), 2.3-2.6 (2H, m, NCH_2CH_2-), 4.80 (2H, d, *J*= 0.9 Hz, C=CH_2), 5.0-5.3 (2H, m, NCH_2-), 7.2-7.6 (3H, m, ArH), 8.2-8.4 (1H, m, ArH)
4c	31 [a]	Reddish oil	$C_{21}H_{21}NS_2$	351.1115 (351.1116)	1.73 (6H, s, CH_3x2), 2.8-3.1 (2H, m, NCH_2CH_2-), 5.1-5.3 (2H, m, NCH_2-), 5.30 (2H, br d, *J*= 18Hz, C=CH_2), 7.2-7.7 (8H, m, ArH), 8.3-8.5 (1H, m, ArH)
5a	67 [a]	Reddish oil	$C_{16}H_{19}NS_2$	289.0959 (289.0959)	1.71 (6H, s, CH_3x2), 1.6-2.3 (4H, m, $NCH_2CH_2CH_2$-), 4.8-5.2 (4H, m, $NCH_2CH_2CH_2CH$=CH_2), 5.6-6.1(1H, m, CH=CH_2), 7.1-7.6 (3H, m, ArH), 8.2-8.4 (1H, m, ArH)
5b	58 [a]	Reddish oil	$C_{17}H_{21}NS_2$	303.1115 (303.1095)	1.72 (6H, s, CH_3x2), 1.77 (3H, s, CH_3),1.8-2.2 (4H, m, $NCH_2CH_2CH_2$-), 4.73 (2H, br s, C=CH_2), 4.9-5.1 (2H, m, NCH_2-), 7.2-7.6 (3H, m, ArH), 8.3-8.5 (1H, m, ArH)
5c	56 [a]	Reddish oil	$C_{22}H_{23}NS_2$	365.1272 (365.1272)	1.69 (6H, s, CH_3x2), 1.7-2.2 (2H, m, NCH_2CH_2-), 2.61 (2H, t, *J*= 7.5 Hz, CH_2CPh=CH_2), 4.9-5.2 (2H, m, NCH_2-), 5.15 (2H, br d, *J*= 17 Hz, C=CH_2), 7.1-7.6 (8H, m, ArH), 8.2-8.4 (1H, m, ArH)
8a	59 [a]	Reddish oil	$C_{21}H_{21}NS_2$	351.1115 (351.1125)	1.71 (6H, s, CH_3x2), 2.5-2.8 (2H, m, NCH_2CH_2-), 5.0-5.3 (2H, m, NCH_2-), 6.14 (1H, dt, *J*= 16, 6 Hz, PhCH=C*H*-), 6.47 (1H, d, *J*= 16 Hz, PhC*H*=CH-),7.0-7.6 (8H, m, ArH), 8.2-8.4 (1H, m, ArH)
8b	61 [a]	Reddish oil	$C_{22}H_{23}NS_2$	365.1272 (365.1274)	1.70 (6H, s, CH_3x2), 1.8-2.1 (2H, m, NCH_2CH_2-), 2.2-2.5 (2H, m, CH_2CH=CHPh), 5.0-5.2 (2H, m, NCH_2-), 6.0-6.6 (2H, m, CH=CH-), 7.1-7.6 (8H, m, ArH), 8.3-8.5 (1H, m, ArH)
8c	41 [a]	Reddish oil	$C_{23}H_{25}NS_2$	379.1428 (379.1432)	1.4-2.0 (4H, m, $NCH_2CH_2CH_2$-), 1.71 (6H, s, CH_3x2), 2.1-2.5 (2H, m, CH_2CH=CHPh), 4.9-5.2 (2H, m, NCH_2-), 6.0-6.5 (2H, m, CH=CH-), 7.1-7.7 (8H, m, ArH), 8.3-8.5 (1H, m, ArH)
11a	25 [b]	Orange oil	$C_{15}H_{17}NOS$	259.1031 (259.1030)	1.6-2.6 (4H, m, CH_2CH_2CH=CH_2), 1.65 (3H, s, CH_3), 3.81 (3H, s, NCH_3), 4.7-5.2 (2H, m, C=CH_2), 5.4-5.9 (1H, m, CH=CH_2), 7.3-7.8 (3H, m, ArH), 8.6-8.8 (1H, m, ArH)
11b	44 [b]	Orange oil	$C_{16}H_{19}NOS$	273.1187 (273.1201)	0.7-1.3 (2H, m, $CH_2CH_2CH_2$-), 1.63 (3H, s, CH_3), 1.5-2.4 (4H, m, $CH_2CH_2CH_2CH$=CH_2), 3.82 (3H, s, NCH_3), 4.7-5.0 (2H, m, C=CH_2), 5.3-5.8 (1H, m, CH=CH_2), 7.1-7.6 (3H, m, ArH), 8.5-8.7 (1H, m, ArH)

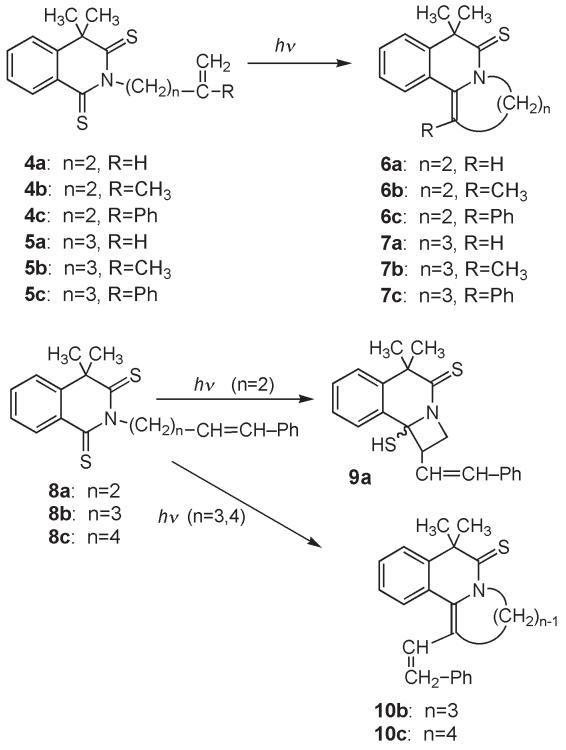
[a] Yield of N-alkylation for dithiohomophthalimide; [b] Yield of monothionation for homophthalimide.

and **7a-c**) were effected by the substituents, increasing in the order of a substituent, -Ph > -CH_3 > -H, at 3- or 4-position in the *N*-alkenyl side chain, in parallel to the stability of each biradical intermediate.

Further, in order to investigate the effect of a phenyl group on photoreactivity, photolysis of dithiohomophtalimide **8** having a terminal styryl group in their *N*-alkyl side chain were also examined. In the case of *N*-(4-phenyl-3-butenyl)dithiohomophthalimide (**8a**), thiol compound (**9a**) only was isolated in 33% yield, in preference to the corresponding Paterno-Büchi products. The formation of **9a** could be explained by the γ-hydrogen abstraction (Norrish type II reaction) at the aromatic thiocarbonyl. We have already shown that the Norrish type II photocyclization took place on the γ-, δ- and ε-carbons relative to the thioimide carbonyl, giving to thiol compounds, in the reaction of the cyclic thioimide having a benzylic hydrogen in the *N*-alkyl side chain [5,6]. But in these systems, the reaction of γ-hydrogen abstraction has predominately given the ketolactam with ring expansion of azetidine ring [7]. Such ring expansion was also observed in the six-membered dithioglutarimide system [4]. Therefore, it is interesting that azetidine-fused compound (**9a**) was isolated without expansion of the azetidine ring in this study. Further, photolyses of **8b** and **8c** gave tricyclic ene-thiolactam compounds (**10b** and **10c**) which arose by elimination of hydrogen sulfide from the initially formed δ- and ε-hydrogen abstraction products (thiols), respectively. Besides the Norrish type II products (**9** and **10**), isolable Paterno-Büchi products were not obtained from a reaction mixture of **8**.

The structures of all products were determined on the basis of spectral and analytical data (Table 2 and Table 3). The mass spectrum (MS) of thiol compound (**9a**) showed the molecular ion peak at *m/z* 351 corresponding to the molecular weight of its starting material (**8a**). Cyclic ene-thiolactams (**6** and **7**) showed molecular ion peaks corresponding to the loss of thioformaldehyde from the corresponding parent thietanes. Conjugated diene compounds

Scheme 2



(**10b** and **10c**) also revealed molecular ion peaks corresponding to the loss of hydrogen sulfide from the corresponding parent thiols.

The addition site of the alkene moiety could easily be distinguished on the basis of ^{1}H-NMR spectra. In the spectra of dithiohomophthalimide (**4**,**5**, and **8**), a signal due to one of the aromatic protons is shifted downfield (δ 8.2-8.5) as compared with the three other aromatic protons, owing to the anisotropic effect of the thiocarbonyl moiety. In the spectra of photoproducts (**6**, **7**, **9a**, **10b**, and **10c**), the signal of aromatic proton disappeared in the lowfield region (under δ 7.9). This suggested that regioselective photoaddition of alkene moiety occurred at the aromatic thiocarbonyl group (1-position). In the ^{13}C-NMR spectra of ene-thiolactams (**6** and **7**), the signals due to the benzylic *sp*^{2} carbon adjacent to a nitrogen atom appeared at δ 122.0-129.5 instead of signals due to aromatic thiocarbonyls in **4** and **5**. Further, for the chemical shift values of the aliphatic thiocarbonyl carbons, the signals in 6-5 ring system (**6**) appeared at lower field (δ 196.6-198.4) in comparison with those in 6-6 ring system (**7**, δ 202.9-204.6). Such difference of chemical shift is also observed in the 5-5 and 5-6 ring system compounds in our group [8].

The ^{13}C-NMR spectra of conjugated diene compounds (**10b** and **10c**) were analogous to those of the ene-thiolactams (**6** and **7**), that is, the singlet peaks due to the *sp*^{2}

Table 2
Physical Properties and Spectral Data for Products (**6,7,9,10** and **12**)

Compd.	Time (h)	Product	Yield (%)	mp (°C)	Appearance (solvent)	IR (Nujol) (cm^{-1})	M(*m/z*) M$^+$	Formula	Analysis Calcd (Found) C	H	N	S
4a	0.33	**6a**	58	138-140	Pale yellow needles		229	$C_{14}H_{15}NS$	73.32 (73.45	6.59 6.65	6.11 6.09	13.98 13.84)
4b	0.1	**6b**	60	153-154.5	Pale yellow needles		243	$C_{15}H_{17}NS$	74.03 (73.95	7.04 7.11	5.76 5.76	13.18 12.90)
4c	0.33	**6c**	68	115-117	Yellow prisms		305	$C_{20}H_{19}NS_2$	78.65 (78.57	6.27 6.30	4.59 4.44	10.50 10.67)
5a	0.83	**7a**	52	98-100	Pale yellow prisms		243	$C_{15}H_{17}NS$	74.03 (73.90	7.04 7.04	5.76 5.60	13.18 13.12)
5b	0.5	**7b**	74	149-151	Colorless prisms		257	$C_{16}H_{19}NS$	74.66 (74.58	7.44 7.45	5.44 5.26	12.46 12.50)
5c	0.75	**7c**	95	183-184.5	Yellow prisms		319	$C_{21}H_{21}NS$	78.95 (78.98	6.63 6.65	4.38 4.24	10.04 9.88)
8a	0.33	**9a**	33	153.5-156	Pale yellow needles	2410	351	$C_{21}H_{21}NS_2$	71.75 (71.49	6.02 6.03	3.98 3.81	18.24 18.03)
8b	1.0	**10b**	54	144-146	Yellow needles		331	$C_{22}H_{21}NS$	79.72 (79.71	6.39 6.35	4.23 4.11	9.67 9.86)
8c	0.83	**10c**	30	161-163	Yellow needles		345	$C_{23}H_{23}NS$	79.96 (79.83	6.71 6.69	4.05 4.08	9.28 9.42)
11a	1.5	**12a-i**	54		Colorless oil	1660	259	$C_{15}H_{17}NOS$		259.1031 [a] (259.1031)		
		12a-ii	18	110-112	Colorless needles	1650	259	$C_{15}H_{17}NOS$	69.46 (69.53	6.61 6.63	5.40 5.38	12.36 12.26)
11b	10.0	**12b-i**	15	129-130	Colorless prisms	1645	273	$C_{16}H_{19}NOS$	70.29 (70.29	7.00 7.02	5.12 5.22	11.73 11.68)
		12b-ii	18	97-97.5	Colorless columns	1630	273	$C_{16}H_{19}NOS$	70.29 (70.29	7.00 7.10	5.12 4.98	11.73 11.85)

[a] Determined by high-resolution mass spectrometry (HR-MS). Upper figure, calcd for M$^+$; lower figure, found.

Table 3

NMR Spectral Data for the Photoproducts **6,7,9,10** and **12**

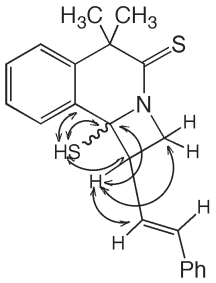
Compd.	^{1}H-NMR ($CDCl_3$, 90 MHz) δ	^{13}C-NMR ($CDCl_3$, 90 MHz) δ
6a	1.78 (6H, s, CH_3x2), 2.6-2.9 (2H, m, NCH_2CH_2-), 4.3-4.5 (2H, m, NCH_2CH_2-), 6.04 (1H, t, *J*=3 Hz, C*H*=C-), 7.2-7.7 (4H, m, ArH)	26.7(t), 33.5(q)x2, 48.2(s), 54.2(t), 110.3(d), 122.4(s), 123.7(d), 126.7(d)x2, 129.8(d), 137.8(s), 140.5(s), 198.4(s)
6b	1.74 (6H, s, CH_3x2), 2.23 (3H, br s, CH_3), 2.6-2.9 (2H, m, NCH_2CH_2-), 4.2-4.4 (2H, m, NCH_2CH_2-), 7.1-7.6 (3H, m, ArH), 7.6-7.8 (1H, m, ArH)	16.1(q), 32.6(q)x2, 34.1(t), 48.0(s), 52.3(t), 124.6(s), 124.7(s), 125.0(d), 126.3(d), 126.5(d), 128.9(d), 131.3(s), 141.4(s), 196.6(s)
6c	1.78 (6H, s, CH_3x2), 3.07 (2H, br t,*J*= 8 Hz, NCH_2CH_2-), 4.45 (2H, br t, *J*= 8 Hz, NCH_2-), 6.8-7.0 (1H, m, ArH), 7.1-7.6 (8H, m, ArH)	32.2(q)x2, 33.0(t), 48.4(s), 52.3(t), 124.2(s), 125.7(d), 126.0(d), 127.2(s), 128.4(d)x2, 129.1(d)x2, 129.6(d), 131.8(s), 136.0(s), 142.1(s), 198.2(s)
7a	1.66 (6H, s, CH_3x2), 1.8-2.1 (2H, m, NCH_2CH_2-), 2.2-2.5 (2H, m, C=C-CH_2-), 4.4-4.6 (2H, m, NCH_2CH_2-), 5.93 (1H, t, *J*= 4 Hz, CH=C-), 7.1-7.6 (4H, m, ArH)	22.0(t), 23.1(t), 29.8(q)x2, 48.4(s), 49.4(t),109.7(d), 123.5(d), 123.9(d), 126.8(d), 128.6(d), 129.5(s), 135.8(s), 139.1(s), 204.6(s)
7b	1.63 (6H, s, CH_3x2), 1.8-2.1 (2H, m, NCH_2CH_2-), 2.12 (3H, s, CH_3), 2.1-2.4 (2H, m, C=C-CH_2-), 4.38 (2H, m, br t, *J*= 6 Hz, NCH_2CH_2-), 7.1-7.5 (4H, m, ArH)	20.8(q), 22.3(t), 28.1(q)x2, 30.2(t), 48.8(s), 49.8(t), 122.0(s), 123.8(d), 125.9(d), 127.5(d), 128.2(d), 130.5(s), 131.9(s), 141.8(s), 202.9(s)
7c	1.76 (6H, s, CH_3x2), 2.0-2.3 (2H, m, NCH_2CH_2-), 2.67 (2H, t, *J*= 6 Hz, C=C-CH_2-), 4.3-4.6 (2H, m, NCH_2CH_2-), 6.5-6.9 (2H, m, ArH), 7.0-7.4 (7H, m, ArH)	22.7(t), 28.3(q)x2, 30.8(t), 48.8(s), 50.2(t), 123.4(d), 125.4(d)x2, 125.5(s), 127.5(d), 128.0(d), 128.7(d)x2, 128.8(d), 129.1(d), 130.6(s), 133.0(s), 141.0(s), 141.5(s), 204.2(s)
9a[a]	1.68 (3H, s, CH_3), 1.94 (3H, s, CH_3), 3.03 (1H, s, SH), 3.9-4.0 (1H, m, C*H*-CH=CH-), 4.45-4.55 (1H, m, NCH_2-), 4.65-4.75 (1H, m, NCH_2-), 6.6-6.7 (2H, m CH=CH-), 7.1-7.6 (9H, m, ArH)	27.6(q), 32.7(q), 47.6(s), 50.2(d), 57.7(t), 80.7(s), 123.1(d), 125.0(d), 125.9(d), 126.8(d)x2, 127.6(d), 128.5(d), 128.9(d)x2, 129.2(d), 135.5(d), 136.2(s), 138.6(s), 141.0(s), 206.8(s)
10b	1.74 (6H, s, CH_3x2), 3.04 (2H, t, *J*= 8 Hz, NCH_2CH_2-), 4.2-4.5 (2H, m, NCH_2-), 6.74 (1H, d, *J*= 15.4 Hz, CH=C*H*Ph), 7.1-7.6 (9H, m, C*H*=CHPh and ArH), 7.6-7.9 (1H, m, ArH)	27.9(t), 31.8(q)x2, 48.8(s), 52.3(t), 122.4(d), 124.9(s), 125.3(s), 125.9(d), 126.7(d), 126.9(d), 128.2(d), 128.9(d), 129.6(d), 132.8(d), 133.5(s), 137.3(s), 142.6(s), 198.2(s)
10c	1.66 (6H, s, CH_3x2), 1.9-2.3 (2H, m, NCH_2CH_2-), 2.68 (2H, t, *J*= 6.5 Hz, C=C-CH_2-), 4.2-4.5 (2H, m, NCH_2-), 6.83 (1H, d, *J*= 16 Hz, CH=C*H*Ph), 7.1-7.6 (10H, m, C*H*=CHPh and ArH)	22.1(t), 24.3(t), 28.4(q)x2, 49.1(s), 51.0(t), 122.2(s), 124.1(d), 126.1(d), 126.6(d), 127.4(d), 127.8(d), 128.9(d), 129.7(d), 130.2(s), 135.7(s), 137.6 (s), 142.3(s), 203.7(s)
12a-i	0.6-1.0 (1H, m, CH_2-), 1.0-2.0 (3H, m, CH_2CH_2CH-), 1.62 (3H, s, CH_3), 2.67 (1H, dd, *J*= 10, 8 Hz, SCH_2CH-), 2.88 (1H, t, *J*= 8 Hz, SCH_2CH-), 3.12 (3H, s, NCH_3), 3.1-3.5 (1H, m, SCH_2CH-), 7.3-7.6 (3H, m, ArH), 8.1-8.3 (1H, m, ArH)	21.7(q), 27.4(t), 28.7(t), 30.9(q), 34.0(t), 47.6(s), 50.2(d), 72.2(s), 123.7(d), 125.2(d), 127.2(d), 128.9(d), 136.9(s), 139.3(s), 175.7(s)
12a-ii	1.2-2.0 (4H, m, CH_2CH_2CH-), 1.68 (3H, s, CH_3), 2.6-3.1 (2H, m, SCH_2CH-), 3.0-3.5(1H, m, SCH_2CH-), 3.58 (3H, s, NCH_3), 7.1-7.5 (4H, m, ArH)	22.3(q), 28.6(t), 30.4(t), 32.6(q), 34.6(t), 47.3(s), 50.9(d), 74.8(s), 122.5(d), 123.5(d), 126.6(d), 127.8(d), 141.5(s), 143.3(s), 174.2(s)
12b-i	0.4-0.8 (1H, m, CH_2-), 0.8-1.8 (4H, m, CH_2CH_2-), 1.70 (3H, s, CH_3), 2.0-2.3 (1H, m, CH_2-), 2.5-2.9 (2H, m, SCH_2CH-), 3.42 (3H, s, NCH_3), 3.3-3.8 (1H, m, SCH_2CH-), 7.3-7.6 (3H, m, ArH), 8.2-8.5 (1H, m, ArH)	26.0(t), 26.3(q), 26.7(t), 29.4(t), 32.1(q), 46.9(s), 47.1(t), 59.9(d), 76.3(s), 125.1(d), 126.9(d), 127.3(d), 129.3(d), 133.7(s), 143.0(s), 174.6(s),
12b-ii	0.4-1.0 (1H, m, CH_2-), 1.2-2.4 (5H, m, $CH_2CH_2CH_2$-), 1.66 (3H, s, CH_3), 2.6-3.1 (2H, m, SCH_2CH-), 3.2-3.6(1H, m, SCH_2CH-), 3.79 (3H, s, NCH_3), 7.3-7.5 (3H, m, ArH), 7.9-8.1 (1H, m, ArH)	25.7(q), 25.7(t), 27.4(t), 30.0(t), 33.9(q), 46.3(s), 47.1(t), 64.4(d), 78.1(s), 125.3(d), 125.7(d), 127.2(d), 128.3(d), 137.3(s), 140.2(s), 176.7(s)

[a] NMR spectra were acquired on JEOL JNM-ECA 500 spectrometer.

carbon atom adjacent to a nitrogen atom and an aliphatic thiocarbonyl carbon appeared at δ 122.2-124.9 and 198.2-203.7, respectively. Moreover, the ^{1}H-NMR spectra of **10b**,**c**, showed the presence of vinyl protons at δ 6.74 (1H, d, *J*= 15.4 Hz for **10b**) and 6.83 (1H, d, *J*= 16.0 Hz for **10c**), respectively. The other vinyl protons were buried in the aromatic region, respectively.

For the thiol compound (**9a**), ^{13}C-NMR spectrum showed peaks due to a quaternary carbon adjacent to a nitrogen and a sulfur atom, a methine carbon, and a thiocarbonyl carbon at δ 80.7 (s), 50.2 (d) and 206.8 (s), respectively. In addition, the ^{1}H-NMR spectrum showed a singlet peak (1H) at δ 3.03, which was assigned to a thiol proton exchangeable with D_2O. In the ^{1}H-^{1}H COSY spectrum, the methine proton signal at δ 3.9-4.0 correlated with both the signals of methylene protons adjacent to a nitrogen atom (δ 4.45-4.55 and 4.65-4.75) and vinyl protons (δ 6.6-6.7). Further, in the HMBC spectrum, a signal of the thiol proton (δ 3.03) correlated with the signals of methine carbon (δ 50.2), quaternary carbon (δ 80.7) adjacent to a nitrogen and a sulfur atom, and aromatic carbon (δ 138.6), respectively. In addition, the methine proton (δ 3.9-4.0) correlated with the signals of methylene carbon (δ 57.7) adjacent to a nitrogen atom, quaternary carbon (δ 80.7) and vinyl carbons (δ 125.0 and 135.5), respectively. Thus, the structure of thiol compound (**9a**) was determined as shown in Scheme 2 and Scheme 3.

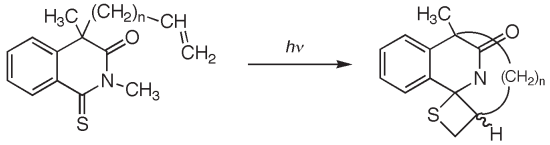
Scheme 3



9a

Next, to investigate the scope of this cyclization reaction, the photoreaction of monothiohomophthalimides (**11a** and **11b**) having an alkenyl substituent at their C-4 position was examined (Scheme 4). As expected, in the photoreaction of **11a** (n=2), [2+2] cycloaddition of the alkene moiety occurred at the thiocarbonyl of 1-position, giving two stereoisomers of bridged-ring compounds (**12a-i** and **12a-ii**) in 54 and 18% yields, respectively. In the case of **11b** (n=3), the photoreaction progressed very slowly to afford a complex photolysate, from which bridged-ring compounds (**12b-i** and **12b-ii**) were obtained in 15% and 18% yields, respectively.

Scheme 4

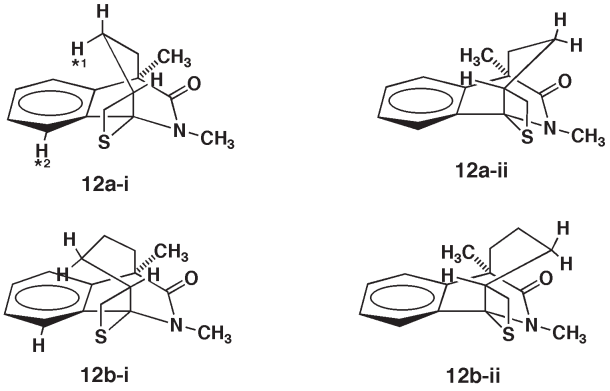


11a: n=2
11b: n=3

12a-i: n=2
12a-ii: n=2
12b-i: n=3
12b-ii: n=3

The structures of products (**12a** and **12b**) were determined on the basis of the spectral and analytical data (Table 2 and Table 3). The MS of bridged-ring compounds (**12a** and **12b**) showed the molecular ion peaks at *m/z* 259 and 273 corresponding to the molecular weights of its starting materials (**11a** and **11b**), respectively. The ^{13}C-NMR spectra of **12** showed peaks due to a benzylic quaternary carbon adjacent to a nitrogen and a sulfur atom, a methylene carbon and a methine carbon in the thietane ring, and a carbonyl carbon at δ 72.2-78.1 (s), 34.0-47.1 (t), 50.2-64.4 (d), and 174.2-176.7 (s), respectively. Further, the ^{1}H-NMR spectra showed signals due to methylene protons and methine proton in the thietane ring at δ 2.5-3.1 (each 2H) and 3.0-3.8 (each 1H), respectively. The stereochemistries of **12-i** and **12-ii** were determined with the aid of the anisotropic effects of the benzene and thietane ring (Scheme 5).

Scheme 5



12a-i **12a-ii**

12b-i **12b-ii**

For **12a-i**, the signal due to a methylene proton (*1) of the cycloheptane ring appeared at upfield (δ 0.6-1.0), owing to an anisotropic effect of the benzene ring. Further, the signal due to the aromatic proton (*2) in **12a-i** showed a downfield shift (δ 8.1-8.3) separated from those of the other aromatic protons (δ 7.3-7.5), indicating that the aromatic proton and thietane ring are close to each other. In the case of its isomer (**12a-ii**), the signal of *N*-methyl protons has shifted to downfield (δ 3.58) as compared with that of **12a-i** (δ 3.12). Since the ^{1}H- and ^{13}C-NMR spec-

tra of **12b-i** and **12b-ii** were analogous to those of **12a-i** and **12a-ii**, respectively, the bridged-ring compounds **12-i** and **12-ii** were assigned for the structures as shown in Scheme 5.

In conclusion, this regioselective photocyclization could provide a useful method for the construction of a variety of ring-fused isoquinoline derivatives, *i.e*., azeto[2,1-*a*]isoquinoline-4-thione (**9a**), pyrrolo[2,1-*a*]isoquinoline-5-thione (**6a-c**, and **10b**), pyrido[2,1-*a*]isoquinoline-6-thione (**7a-c**, and **10c**), and bridged-ring compounds having ring systems, 4-6-6-7 (**12a**) and 4-6-6-8 (**12b**), otherwise inaccessible by conventional thermal reaction.

EXPERIMENTAL

All melting points were determined on a Yamato melting point apparatus (model MP-21) and are uncorrected. Infrared spectra were recorded on a JASCO A-102 spectrometer. Nuclear magnetic resonance spectra were taken on JEOL-FX-90Q and JEOL JNM-ECA 500 spectrometers. Chemical shifts are reported in ppm (δ) with tetramethylsilane as an internal standard. The abbreviations used are as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dt, doublet of triplets. Mass spectra were determined with a JEOL JMS-QH-100 gas chromatograph-mass spectrometer with a direct inlet system and high-resolution MS (HRMS) were recorded using a Micromass Auto Spec 3000 mass spectrometer. Irradiations of substrates were conducted using a 500 W high-pressure mercury lamp and a water-cooled quartz immersion well (Eikosha EHB-W-500). Stirring of the reaction mixture was effected by the introduction of a stream of nitrogen at the bottom of the outer jacket. All column chromatography was conducted using silica gel (Wakogel C-300, 200-300 mesh).

1,2,3,4-Tetrahydro-2-(3-butenyl)-4,4-dimethyl-1,3-dithioxoisoquinoline [*N*-(3-Butenyl)-4,4-dimethyl-1,3-dithiohomophthalimide (**4a**)].

Typical Procedure.

i) A solution of homophthalic anhydride (884 mg, 5.46 mmol) in dimethoxyethane (DME, 30 ml) was added dropwise at 0 °C to a suspension of NaH (288 mg, 12 mmol) in DME (20 ml) under an Ar atmosphere, and the reaction mixture was stirred at the same temperature for 15 min. Then methyl iodide (8 ml) was added dropwise to the above mixture at room temperature, and the mixture was refluxed for overnight. Then 10% KOH solution (4.5 ml) was added to the above mixture at room temperature, and the mixture was stirred for an additional 3 h at the same temperature. The reaction mixture was poured into ice-water, acidified with dil. HCl, and extracted with Et_2O-AcOEt. The organic layer was washed with brine and dried over $MgSO_4$, and evaporated to dryness. A mixture of the resulting dicarboxylic acid and 28% NH_4OH solution (1 ml) in acetone (10 ml) was stirred at room temperature for 5 min, then the solvent was evaporated *in vacuo*, and the residue was fused at 200 °C for 90 min. The residue was chromatographed on silica gel with AcOEt-hexane (1:4, v/v) to give 4,4-dimethyl-1,3-dioxoisoquinoline (4,4-dimethylhomophthalimide: 532 mg, 52%). Colorless needles (from AcOEt-hexane), mp 125.0-126.5 °C. IR (Nujol): 3190, 3200 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.66 (6H, s, CH_3x2), 7.2-7.8 (3H, m, ArH), 8.1-8.3 (1H, m, ArH), 8.4-8.7 (1H, m, NH). MS *m/z*: 189 (M^+).

ii) A solution of 4,4-dimethylhomophthalimide (189 mg, 1 mmol) and Lawesson's reagent (606 mg, 1.5 mmol) in toluene (6 ml) was refluxed for 1.5 h. After reaction, the solution was directly subjected to column chromatography on silica gel with AcOEt-hexane (1:4, v/v) to give 4,4-dimethyldithiohomophthalimide (218 mg, 99%). Orange needles (from AcOEt-hexane), mp 117.5-119.0 °C. IR (Nujol): 3140 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.81 (6H, s, CH_3x2), 7.4-7.7 (3H, m, ArH), 8.4-8.6 (1H, m, ArH), 10.9-11.3 (1H, m, NH). MS *m/z*: 221 (M^+).

iii) A solution of diethyl azodicarboxylate (418 mg, 2.4 mmol) in THF (3 ml) was added dropwise under an Ar atmosphere to a stirred mixture of 4,4-dimethyldithiohomophthalimide (442 mg, 2 mmol), 3- buten-1-ol (216 mg, 3 mmol), and triphenylphosphine (630 mg, 2.4 mmol) in THF (12 ml) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, then the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with AcOEt-hexane (1:40, v/v) to give **4a** (359 mg, 65%). Compounds **4b**, **4c**, **5a-c**, and **8a-c** were prepared from 4,4-dimethyldithiohomophthalimide and the corresponding alcohols, respectively, according to the procedure described above. The solvent systems used in column chromatography were as follows: **4b**, **5a**, and **8c**, AcOEt-hexane (1:30, v/v); **4c**, **5b**, **5c**, and **8a**, AcOEt-hexane (1:40, v/v); **8b**, AcOEt-hexane (1:20, v/v). The yields of *N*-alkylation and analytical data for dithiohomophthalimides **4**,**5**, and **8** are listed in Table 1.

1,2,3,4-Tetrahydro-4-(3-butenyl)-2,4-dimethyl-3-oxo-1-thioxoisoquinoline [4-(3-Butenyl)-2,4-dimethyl-3-oxo-1-thiohomophthalimides (**11a**)].

Typical Procedure.

i) A solution of *N*-methylhomophthalimide (5.25 g, 30 mmol) in DME (40 ml) was added dropwise at room temperature to a suspension of NaH (720 mg, 30 mmol) in DME (90 ml) under an Ar atmosphere, and the reaction mixture was stirred at the same temperature for 10 min. Then 4-bromo-1-butene (4.5 ml, 44 mmol) was added dropwise to the above mixture, and the mixture was refluxed for 4.5 h. After reaction, sat. NH_4Cl solution was added to the mixture, which was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel with AcOEt-hexane (1:6, v/v) to give 1,2,3,4-tetrahydro-4-(3-butenyl)-2-methyl-1,3-dioxoisoquinoline [4-(3-butenyl)-2-methylhomophthalimide: 1.81 g, 26%]. Colorless oil IR (Nujol): 1710, 1665 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.7-2.4 (4H, m, CH_2CH_2CH=CH_2), 3.35 (3H, s, NCH_3), 3.97 (1H, t, *J*= 5 Hz, ArCHCON-), 4.7-5.1 (2H, m, CH=CH_2), 5.4-5.9 (1H, m, C*H*=CH_2), 7.2-7.8 (3H, m, ArH), 8.1-8.3 (1H, m, ArH). MS *m/z*: 229 (M^+).

ii) A solution of 4-(3-butenyl)-2-methylhomophthalimide (1.81 g, 7.9 mmol) in DME (10 ml) was added dropwise at room temperature to a suspension of NaH (240 mg, 10 mmol) in DME (50 ml) under an Ar atmosphere, and the reaction mixture was stirred at the same temperature for 10 min. Then CH_3I (5 ml, 80 mmol) was added dropwise to the above mixture, and the mixture was refluxed for 40 min. Then sat. NH_4Cl solution was added to the mixture, and the aqueous mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$, and evaporated to give 4-(3-butenyl)-2,4-dimethyl-

homophthalimide (1.91 g, 99%). Colorless oil. IR (Nujol): 1705, 1660 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 1.63 (3H, s, CH_3), 1.5-1.8 (2H, m, C*H*$_2$CH$_2$-), 1.9-2.6 (2H, m, C*H*$_2$CH=CH$_2$), 3.37 (3H, s, NCH_3), 4.5-5.0 (2H, m, CH=C*H*$_2$), 5.4-5.8 (1H, m, C*H*=CH$_2$), 7.3-7.8 (3H, m, ArH), 8.1-8.4 (1H, m, ArH). MS *m/z*: 243 (M^+).

iii) A solution of 4-(3-butenyl)-2,4-dimethylhomophthalimide (1.41 g, 5.8 mmol) and Lawesson's reagent (3.5 g, 8.7 mmol) in toluene (50 ml) was refluxed for overnight. The solution was directly subjected to column chromatography on silica gel with AcOEt-hexane (1:10, v/v) to give 1,2,3,4-tetrahydro-4-(3-butenyl)-2,4-dimethyl-3-oxo-1-thioxoisoquinoline (**11a**, 370 mg, 25%). Orange oil. IR (neat): 1700 cm^{-1}.

Compound **11b** was obtained by the same method as described for the preparation of **11a**, using 5-bromo-1-pentene in place of 4-bromo-1-butene. The yields of thionation and analytical data for monothiohomophthalimides **11a** and **11b** are listed in Table 1.

Irradiation of Thiohomophthalimide Derivatives (**4,5,8,** and **11**).

General Procedure.

A solution of thiohomophthalimide (5 mM) in MeCN was irradiated with a 500 W high-pressure mercury lamp through a Pyrex filter with water cooling. After removal of the solvent *in vacuo*, the residue was subjected to silica gel column chromatography. The solvent systems used were as follows: **4a**, **4c**, **5a**, **5c**, and **8a-c**, AcOEt-hexane (1:20, v/v); **4b**, AcOEt-hexane (1:30, v/v); **5b**, AcOEt-hexane (1:40, v/v); **11a**, (1:5, v/v); **11b**, (1:10, v/v). The yields and analytical data for photoproducts **6**,**7**,**9**,**10**, and **12** are listed in Table 2 and Table 3.

Acknowledgements.

We thank S. Nomura and K. Iwashita (nee Ohnishi) for their technical assistance in some of the experiments. We are also grateful to Center for Instrumental Analysis, Hokkaido University for measurement of elemental analysis.

REFERENCES AND NOTES

[1] M. Machida, K. Oda, E. Yoshida, and Y. Kanaoka, *J. Org. Chem*., **50**, 1681 (1985).

[2] M. Machida, K.Oda, E. Sato, and Y. Kanaoka, *J. Synth. Org. Chem. Japan* (Yuki Gosei Kagaku Kyoukai Shi), **44**, 1071 (1986).

[3] K. Oda, T. Ishioka, Y. Fukuzawa, N. Nishizono, and M. Machida, *Heterocycles*, **53**, 2781 (2000) and references cited therein.

[4] H. Takechi, M. Machida, and Y. Kanaoka, *Synthesis*, 778 (1992).

[5a] H. Takechi, M. Machida, and Y. Kanaoka, *Chem. Pharm. Bull*., **37**, 1431 (1989); [b] H. Takechi and M. Machida, *Chem. Pharm.Bull*., **45**, 1 (1997); [c] H. Takechi. H. Takahashi, R. Mahara, and M. Machida, *Heterocycles*, **59**, 303 (2003).

[6a] M. Machida, K. Oda, and Y. Kanaoka, *Tetrahedron Lett.*, **26**, 5173 (1985); [b] K. Oda, M. Machida, and Y. Kanaoka, *Chem. Pharm. Bull* ., **34**, 4406 (1986).

[7a] M. Machida, H. Takechi, Y. Shishido, and Y. Kanaoka, *Synthesis*, 1078 (1982); [b] H. Takechi, S, Tateuchi, M. Machida, Y. Nishibata, K. Aoe, Y. Sato, and Y. Kanaoka *Chem. Pharm. Bull*., **34**, 3142 (1986) and references cited therein.

[8] M. Machida, K. Oda, and Y. Kanaoka, *Chem. Pharm. Bull* ., **32**, 75 (1984).