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Author	山本, 有一(Yamamoto, Yuichi) 与田, 玲子(Yoda, Reiko) 小口, 敬子(Koguchi, Kyoko)
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**Studies on Thiazoline Derivatives (XV)**  
**Reactions of 2-Phenyl and 2-Methylamino-2-thiazolines**  
**with Methyl and Phenylisothiocyanates**

YUICHI YAMAMOTO, REIKO YODA, and KYOKO KOGUCHI

山本有一, 与田玲子, 小口敬子

(Received September 30, 1978)

Summary

As a secondary amine, 2-methylamino-2-thiazoline (1b) or 2-phenylamino-2-thiazoline (1c) reacted with methylisothiocyanate (2b) or phenylisothiocyanate (2c), as shown in Scheme I, regardless of R, R' = alkyl or aryl to give 3-[N-methyl- (or phenyl)thiocarbamoyl]-2-methyl (or phenyl)iminothiazolidine (3c, d, e), but not the compound (4). There was no thermal rearrangement of (3) to (4).

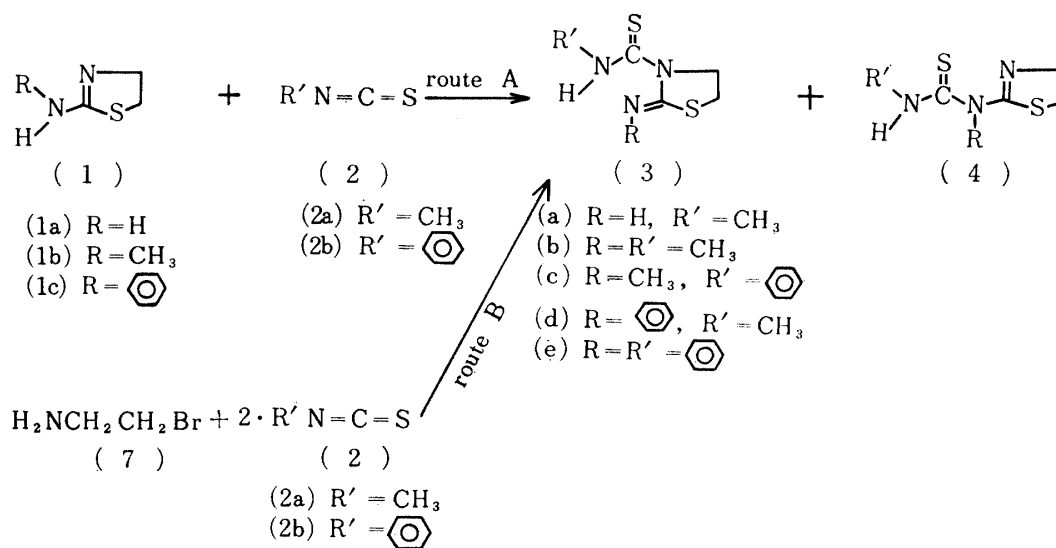
The authors<sup>1)</sup> reported previously that 2-amino-2-thiazoline (1a) reacted with methylisothiocyanate (2a) under 40°C to give 3-(N-methylthiocarbamoyl)-2-iminothiazolidine (3a) which isomerized to thermodynamically more stable 2-(N-methylthiocarbamoyl)-amino-2-thiazoline (4a).

It was reported that the reaction of (1a) with phenylisothiocyanate (2b) gave 3-(N-phenylthiocarbamoyl)-2-iminothiazolidine (3c) under 50°C and (3c) thermally isomerized to 2-(N-phenylthiocarbamoyl)amino-2-thiazoline (4c).<sup>2)</sup> Later it was confirmed that only (4c) was obtained regardless of the reaction temperature.<sup>3)</sup>

The authors<sup>4)</sup> reported earlier that a secondary amine, 2-methylamino-2-thiazoline (1b), reacted with (2a) to give only 3-(N-methylthiocarbamoyl)-2-methyliminothiazoline (3b), but not the isomeric 2-(N-methylthiocarbamoyl)methylamino-2-thiazoline (4b) and that there was no thermal isomerization of (3b) to (4b).

This report has clarified the reaction between the secondary amines (1b, c) and phenylisothiocyanate (2b). It was reported that the reaction between (1c) and (2b) gave 2-(N-phenylthiocarbamoyl)phenylamino-2-thiazoline (4c),<sup>5)</sup> however, we have shown

- 1) Y. Yamamoto and R. Yoda, Annual Report Kyoritsu Pharm. College., 18, 53 (1973); C.A., 81, 136039z (1974)
- 2) E. Fromm and Kapeller-Alder, Ann. Chem., 467, 259 (1928)
- 3) D.L. Klayman, J.J. Maul and George W.A. Milne, J. Hetero. Chem., 5, 520 (1968)
- 4) Y. Yamamoto, R. Yoda and M. Matsumura, Chem. Pharm. Bull. (Tokyo) 23, 2134 (1975)
- 5) E. Cherbuliez, Br. Baehler, S. Jaccard, H. Jindra, G. Weber, G. Wyss and J. Rabinowitz, Hel. Chem. Acta., 49, 807 (1966)



Scheme I

from NMR and chemical data that the product was 3-(N-phenylthiocarbamoyl)-2-phenyliminothiazolidine (3e).

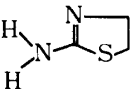
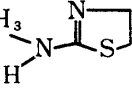
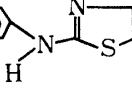

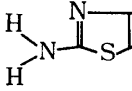
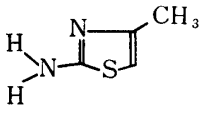
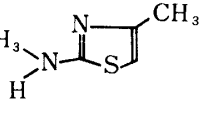
As shown in Table I, the difference of pKa values for 2-amino-2-thiazolidine (1a) and its secondary amine (1b) are larger than those of thiazole amines. The basicity of (1a) and (1b) are similar and a steric effect of N-methyl group in (1b) may be considered for the reaction. On the other hand, the aromatic secondary amine (1c) has a smaller pKa value than (1a, b) and is less basic, therefore, the nucleophilic activity of (1c) with (2a, b) is weaker than that of (1a, b) and a steric hindrance of phenyl group may be considered.

The reaction of (1c) with (2a) should provide either (3d) or its isomer (4d). Equimolar amounts (8.4 mmol) of (1c) and (2a) were refluxed for 2 hr. in dry toluene to give a yellow oily residue after evaporating the solvent which crystallized on cooling, m.p. 118-121° (crude). Recrystallization (EtOH) gave (3d), m.p. 123-124°. As shown in Table II, R<sub>f</sub> value (TLC) of (3a) is larger than (4a) and (4c), and is close to the known (3a) and (3b).

As shown in Table III, NMR data of (3d) indicated a chemical shift of 4.82 ppm (t, J=7.0Hz, 2H) for N-CH<sub>2</sub>, showing a lower field shift of 0.87 ppm than that of (1c). The authors<sup>1),6)</sup> already pointed out that a low field shift of 0.80-0.90 ppm for -N-CH<sub>2</sub> at the position of 4 in the thiazolidine when an electron-withdrawing group such as thiocarbamoyl is attached at 3-N of 2-thiazolidine. Therefore, (3d) seems to belong to the structure (3).

6) Y. Yamamoto, R. Yoda and S. Kouda, Annual Report Kyoritsu Pharm. College, 18, 46(1973); C. A., 81, 120524t (1974)

Table I pKa Values of (1a, b, c) and related compounds

structure	pKa	solvent	temperature (°C)
(1 a) 	8.67 ± 0.03	H <sub>2</sub> O	24
(1 b) 	8.66 ± 0.03	H <sub>2</sub> O	24
(1 c) 	7.20 <sup>8)</sup>		
	2.5 <sup>7)</sup>	H <sub>2</sub> O	20–25
	5.40 <sup>7)</sup> 5.75 ± 0.02	H <sub>2</sub> O	26
	5.81 <sup>7)</sup> 5.75 ± 0.02	H <sub>2</sub> O	24
	5.90 ± 0.03	H <sub>2</sub> O	23

7) M. Nagano, J. Tobitsuka, T. Matsui and K. Oyamada; Chem. Pharm. Bull. (Tokyo), 20, 2618 (1972)

8) H.Najer *et al.*; C. R. Acad. Sc. paris, t 260 (1965) 4343

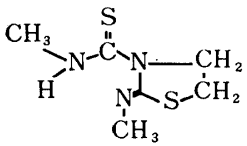
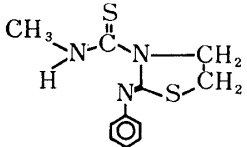
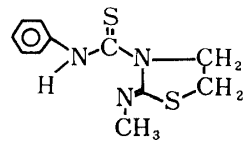
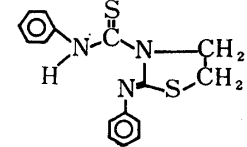
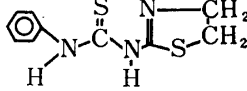
When (3d) is refluxed in 15% H<sub>2</sub>SO<sub>4</sub>, it gave colorless crystals of m.p. 137° (EtOH). Its IR spectra showed a sharp strong band at 1700cm<sup>-1</sup> and was identified as 3-(N-methylthiocarbamoyl)thiazolidine-2-one (5d)<sup>2)</sup> from IR and mixed m.p.. Therefore, the structure of (3d) was established to be 3-(N-methylthiocarbamoyl)-2-phenyliminothiazolidine.

The reaction of 2-methylamino-2-thiazoline (1b) with phenylisothiocyanate (2c) may give 3-(N-phenylthiocarbamoyl)-2-methyliminothiazolidine (3c). An equimolar (1b) and (2c) reacted to give crystals (3) with m.p. 70–71° (EtOH). The R<sub>f</sub> value

Table II Physical Constants of Compounds

Compnd.	m.p. (recrys.)	Found (Calcd.) (%) C : H : N	IR (KBr disk) 1650-1500cm <sup>-1</sup>	$\lambda_{\text{max}}^{\text{IPA}} \text{ nm} (\epsilon \times 10^{-2})$	TLC (Rf Value) cyclohexane 1 CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub> 1 CHCl <sub>3</sub>
	66° (EtOH)		1634 1572 1566	266.0(180) 239.0(sh)	0.63 0.45
	123-124° (MeOH-H <sub>2</sub> O)	52.74, 5.06, 16.96 (52.56, 5.21, 16.72)	1605(s) 1568(s) 1601(s) 1500(s) 1589(s)	275.0(183) 246.0(125)	0.65 0.36
	70-71° (EtOH)	52.51, 5.12, 16.69 (52.56, 5.21, 16.72)	1620(s) 1550(s) 1603(m) 1540(s) 1590(m) 1530(s)	300.0(74) 270.0(119) 224.5(131)	0.56 0.39
	116-117° (MeOH)	61.33, 4.61, 13.44 (61.31, 4.82, 13.41)	1593(s) 1520(s) 1570(s) 1540(s)	268.5(187) 225.0(181)	0.63 0.48
	150-152° (CH <sub>3</sub> CN)		1615(w.sh) 1595(s.sh) 1580(s) 1570(s) 1516(s) 1510(s)	331.5(76) 300.5(171)	0.36 0.10

Table III NMR Spectral Data by JNM-NH 100 (100MHz)

Compd.	N-CH <sub>2</sub>	CH <sub>2</sub> -S	=N-CH <sub>3</sub>	N-CH <sub>3</sub>	NH
3b 	4.65 t, J=7.0 Hz 2 H	3.14 t, J=7.0 Hz 2 H	3.14 s, 3 H		14.16 s, 1 H
3d 	4.82 t, J=7.0 Hz 2 H	3.10 t, J=7.0 Hz 2 H		3.18 d, J=5.0 Hz 3 H	11.98 s, 1 H
3c 	4.82 t, J=7.0 Hz 2 H	3.14 t, J=7.0 Hz 2 H	3.14 s, 3 H		14.16 s
3e 	4.85 t, J=7.0 Hz 2 H	3.10 t, J=7.0 Hz 2 H			13.80
4c 	3.47 m	3.23 m			9.22 10.32

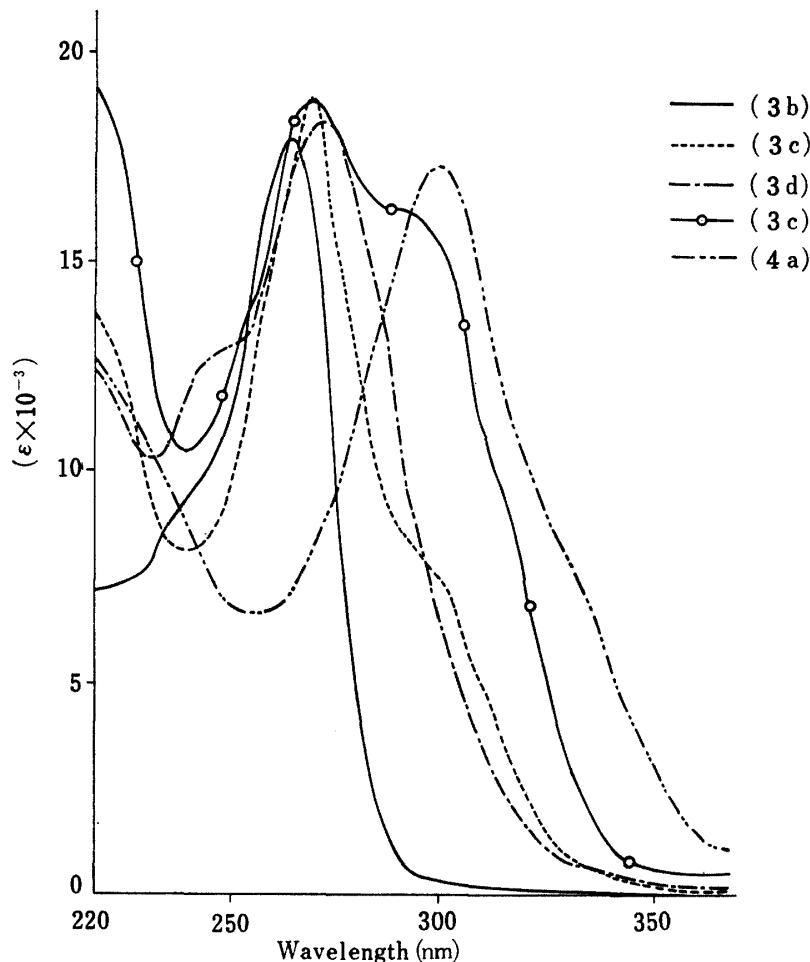
The NMR Spectral data were measured at room temperature in CDCl<sub>3</sub>.  
Chemical shifts are expressed in  $\delta$  (ppm) with TMS as internal standard.

(TLC) is similar to (3d). NMR data showed a chemical shift of 4.82 ppm (t, J=7.0 Hz, 2H) for N-CH<sub>2</sub> which was same position with (3d) suggesting the structure (3). The hydrolysis of (3c) in 15% H<sub>2</sub>SO<sub>4</sub> gave (1b) by elimination (2b). (2b) showed a characteristic  $\nu_{N=C=S}$  absorption at 2130 cm<sup>-1</sup> (IR) and (1b) was identified by IR and as its picrate.

E. Cherbuliez *et al.*<sup>5)</sup> heated (1c) and (2b) at 120°C for 2 hr. without solvent and the resulting crystals were recrystallized (MeOH), m.p. 112-113° and assigned as 2-(N-phenylthiocarbamoyl)phenylamino-2-thiazoline (4c).

The authors refluxed equimolar quantities of (1c) and (2b) in toluene the resulting product was recrystallized from EtOH to give colorless needles (3e), m.p. 116-117°. The product obtained by Cherbuliez's method gave an identical (3e) of m.p. 116-117° (EtOH). The R<sub>f</sub> value (TLC) of the product (3e) is similar to those of (3c) and (3d) and the NMR data showed a chemical shift of 4.85 ppm (t, J=7.0Hz, 2H) which is

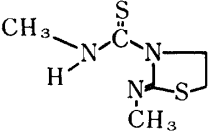
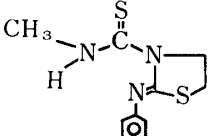
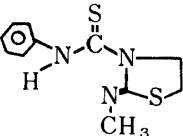
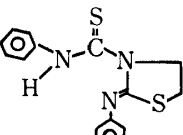
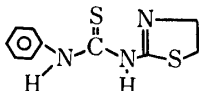
Fig. I UV Absorption Spectra of (3b), (3c), (3d), (3e) and (4a) in propanol-2 for Spectroscopy (MERCK)



close to those of (3c) and (3d). The elemental analysis agreed with  $C_{16}H_{15}N_3S_2$  and the IR spectra showed  $\nu_{C=N}$  and  $\nu_{\text{C=C}}$  absorptions at  $1593$  (s) and  $1570$   $\text{cm}^{-1}$  (s). The C=N absorption shifted to lower frequency due to the conjugation with phenyl group. As shown in Fig. I, UV absorption curves of (3c) and (3b) are similar. The  $273$  nm ( $\epsilon=18300$ ) band of (3d) corresponds with  $270$  nm ( $18300$ ) of (3e). (3c), (3e) and (4a) all having N-phenylthiocarbamoyl group have an absorption at  $300$  nm. The absorption curve of (3e) is very different from that of (4a). As shown in Scheme I, (3e) was obtained from 1 mole of 1-amino-2-bromoethane (7) and 2 moles of (2b). As shown in Table IV, Mass spectral data indicated that the fragmentation of known (4c) and (3e) are quite different. (4c) showed  $M^+$  at  $m/e$  237 (74.12%),  $[\text{C}_6\text{H}_5\text{-N=C=S}]^+$  at  $m/e$  137 (base) and  $[\text{C}_6\text{H}_5]^+$  at  $m/e$  77 (44.4%).

On the other hand, (3e) showed no  $M^+$  at  $m/e$  313, but showed  $[M^+ - \text{C}_6\text{H}_5\text{-N=C=S}]$  at  $m/e$  177 (91.4%),  $[\text{C}_6\text{H}_5\text{-N=C=S}]^+$  at  $m/e$  135 (base) and  $[\text{C}_6\text{H}_5]^+$  at  $m/e$  77 (base).

Table IV Mass Spectral Data m/e (Relative Intensity : %)

Compd.	M <sup>+</sup>	M <sup>+</sup> -SH	M <sup>+</sup> -RN=C=S		RN=C=S
3b 	189 (84)	156 (1.1)	116 (base)	115 (88)	73 (18)
3d 	251 (70.93)	—	178 (50)	177 (base)	73 (23.58)
3c 	251 (8.8)	—	116 (60.3)	115 (base)	135 (61.0)
3e 	—	—	177 (91.4)	—	135 (base)
4c 	237 (74.1)	204 (8.1)	102 (33.8)	101 (10.6)	135 (base)

When (3e) was hydrolyzed with 15% H<sub>2</sub>SO<sub>4</sub>, it gave the products shown in Scheme II. As was the case for the hydrolysis of (3c) the liberation of (2b) took place quickly and (1c) was obtained as crystals when the aqueous layer was neutralized. The hydrolysis product aniline was detected by a color reaction. (2b) was identified with IR and (1c) was confirmed with IR and mixed m.p..

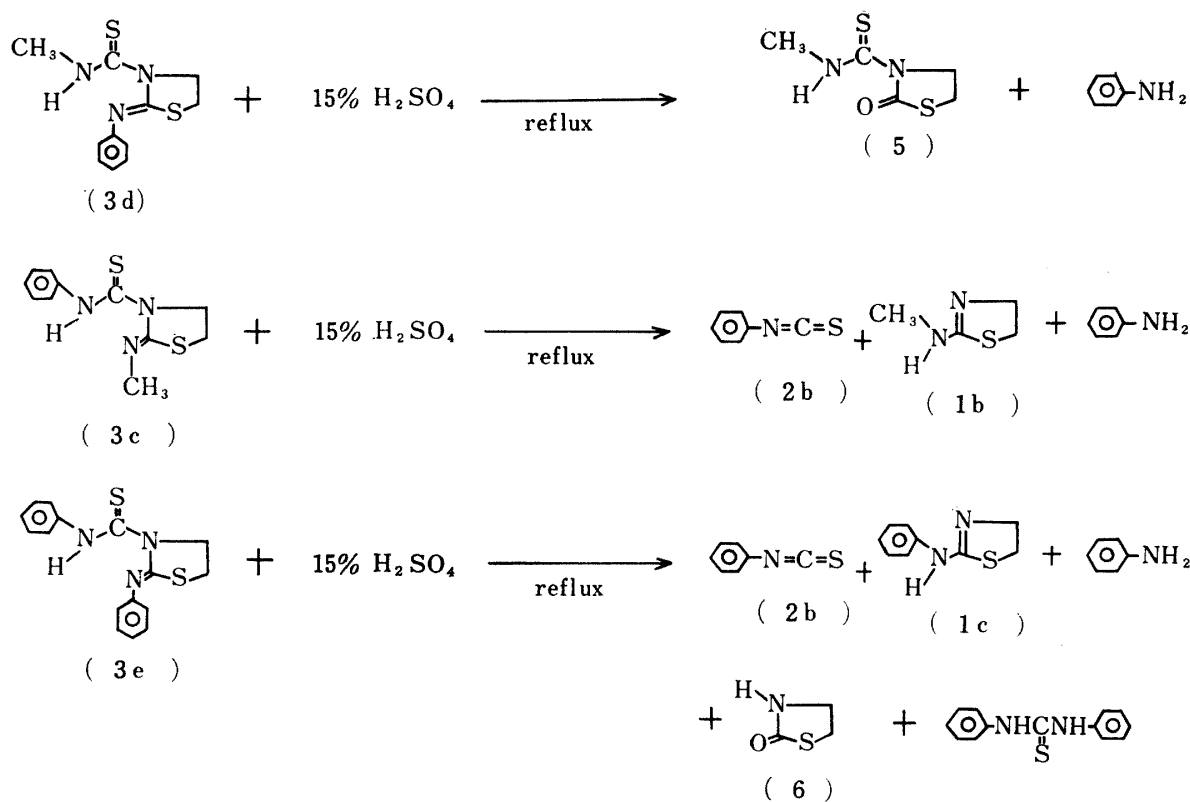
#### Conclusion

As for the reaction between (1) and (2), 2-amino-2-thiazoline (1a) as a primary amine (R=H) reacted with alkylisothiocyanate (2a) to give an unstable product (3a) which isomerized to (4a) upon heating. However, (1a) with arylisothiocyanate (2b) gave only stable (4c).

2-methylamino-2-thiazoline (1b) as a secondary amine (R=CH<sub>3</sub>) reacted with (2) (R'=alkyl or aryl) to give only (3) which did not isomerize upon heating.

2-phenylamino-2-thiazoline (1c) as an aromatic secondary amine (R=C<sub>6</sub>H<sub>5</sub>) reacted with (2) (R'=alkyl or aryl) to give only (3d) or (3e).





Scheme II

## Experimental

Infrared spectra were obtained a Hitachi EPI-G3 spectrometer, ultraviolet spectra with a Shimadzu 200-S automatic recording spectrometer, nuclear magnetic resonance spectra with a Nihon Denshi TMS-OSG (70eV) and high mass resolution spectra with a Nihon Denshi JMS 01 SG-2 HI-resolution massspectrometer.

Typical experimental procedure is illustrated below ;

**3-(N-phenylthiocarbonyl)-2-phenyliminothiazolidine (3e)**

**route A** A toluene solution (30 ml) of 2-phenylamino-2-thiazoline (1 g, 0.0056 mol) and phenylisothiocyanate (1.52 g, 0.0112 mol) was refluxed for 2 hr. The toluene solution was evaporated to give crude (3e), which was recrystallized from ethanol to afford pure (3e).

**route B** To a mixture of cold 33% aq. KOH (100 ml) and benzene (100 ml) was added bromoethylamine·HBr (33.2 g) with stirring. The benzene layer was separated and the aqueous layer was extracted with benzene (50 ml×2). To the combined benzene solution was added dropwise phenylthiocyanate (16 g) under ice-cooling, and then the mixture was refluxed for 2 hr. A viscous oily layer produced during the reaction was separated from the benzene layer and the benzene layer was extracted with H<sub>2</sub>O. The aqueous layer was treated with conc. KOH (33%) to give white crystalline 2-ph-

enylamino-2-thiazoline (1c). The benzene layer evaporated *in vacuo* to leave a white solid (3e), which was recrystallized from methanol to afford pure (3e).

**Hydrolysis of (3)**

An aqueous HCl solution (15%, 20 ml) of (2a) was heated at about 110°. Just dissolving (3) in an aq. HCl solution, the oily substance was separated, and after being kept at room temperature for several hr. The solution was extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> layer was dried over MgSO<sub>4</sub>, and was evaporated to give oil (2b). The aqueous layer was treated with an aqueous NaHCO<sub>3</sub> to afford (1c, 0.25 g).