CYCLOADDITION IN SYNTHESIS OF SULFONAMIDE DERIVATIVES. VI[1]

UNEXPECTED PRODUCTS FROM THE REACTION OF DITHIOCARBAMATE WITH CHLOROSULFONYL ISOCYANATE

A NOVEL SYNTHETIC ROUTE TO 5-AMINO-1,2,4-DITHIAZOL-3-ONE AND *N*,*N*-DISUBSTITUTED *N'*-CHLOROSULFONYLCARBAMIMIDOYL CHLORIDE

Tsuneo Iwakawa*[a], Tomohiro Sato[b], and Akira Murabayashi [a]

a) Aburahi Laboratories, Shionogi & Co., Ltd., Koka-cho, Koka-gun, Shiga 520-34 Japan b) Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

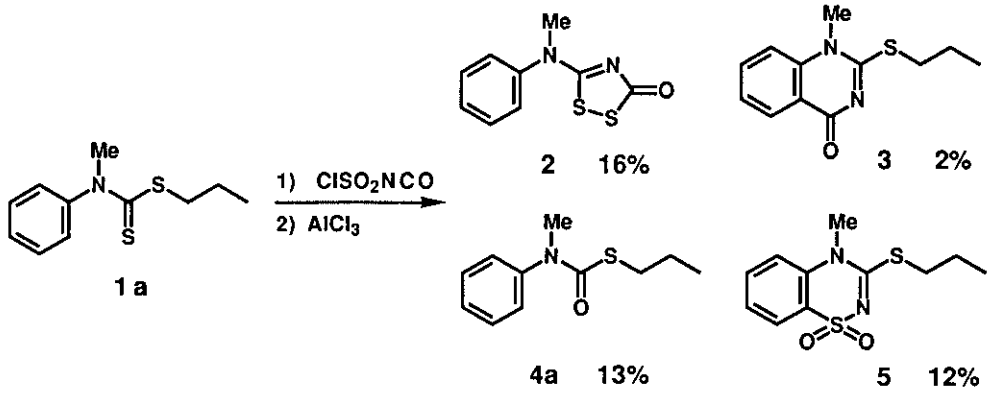
Abstract- Reaction of propyl *N*-methyl-*N*-phenyldithiocarbamate (**1a**) with chlorosulfonyl isocyanate in the presence of $AlCl_3$ gives 5-(*N*-methylanilino)-1,2,4-dithiazol-3-one (**2**), 1-methyl-2-propylthio-4-quinazolinone (**3**) and *N*-methyl-*N*-phenyl-*S*-propylthiocarbamate (**4a**) in addition to 3-propylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5**). However, the same reaction conducted without $AlCl_3$ gives **2**, **4a**, and (*Z*)-*N*-methyl-*N*-phenyl-*N'*-chlorosulfonylcarbamimidoyl chloride (**6**). Compound (**2**) exhibited fungicidal and antibacterial activities.

In a previous paper of this series, we reported the synthesis of *N*-(*C*-aminoalkylthiomethylene)-benzenesulfonamide by using a novel [2+2] cycloaddition reaction of sulfonyl isocyanate with dithiocarbamate.[2] To further explore the utility of this reaction, we developed a one-pot synthesis of several heterocyclic compounds which bear the sulfonamide moiety by the [2+2] cycloaddition reaction of chlorosulfonyl isocyanate (CSI) with dithiocarbamate or thiocarbamate as a key

step.[3]

In the course of these studies, we found an unexpected reaction of CSI with dithiocarbamate which led to a novel one-step synthesis of 5-amino-1,2,4-dithiazol-3-one (**2**) and *(Z)-N*-phenyl-*N*-methyl-*N'*-chlorosulfonylcarbamimidoyl chloride (**6**). In the present paper, we describe the above findings in detail.

The one-pot synthesis of several heterocyclic compounds descrived above gave somewhat low yields of 3-alkylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxides because of a side reaction. Therefore, we tried to isolate these by-products and to determine their structures. The dithiocarbamates (**1**) were prepared from the corresponding amines and alkyl halides by a previously reported method.[2] Propyl *N*-methyl-*N*-phenyldithiocarbamate (5.0 mmol) in 1,2-dichloroethane (10 ml) was stirred at 60°C with CSI (8.0 mmol) for 30 min, followed by treatment with $AlCl_3$ for 1 h at room temperature. The reaction mixture was further stirred for 30 min at 60°C and 5-(*N*-methylanilino)-1,2,4-dithiazol-3-one (**2**) (16% yield), 1-methyl-2-propylthio-4-quinazolinone (**3**) (2% yield) and *N*-methyl-*N*-phenyl-*S*-propylthiocarbamate (**4a**) (13% yield) were obtained in addition to 3-propylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5**) (12% yield) (Scheme 1).



Scheme 1

The structures of these products were supported by their elemental analyses and spectral data (ms,^{1}H-nmr,^{13}C-nmr). The structure of **2** was confirmed by X-ray analysis (Figure 1).[4]

In order to establish the correct structure of **3**, we synthesized **3** by an independent route by using [2+2] cycloaddition of *N*-(chlorocarbonyl) isocyanate with propyl *N*-methyl-*N*-phenyldithiocarbamate, followed by Friedel-Crafts cyclization (Scheme 2).

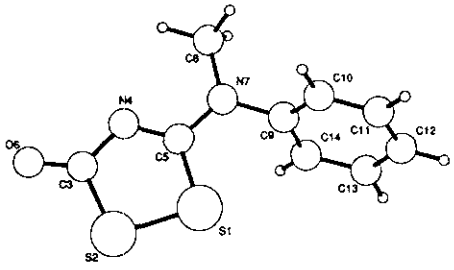
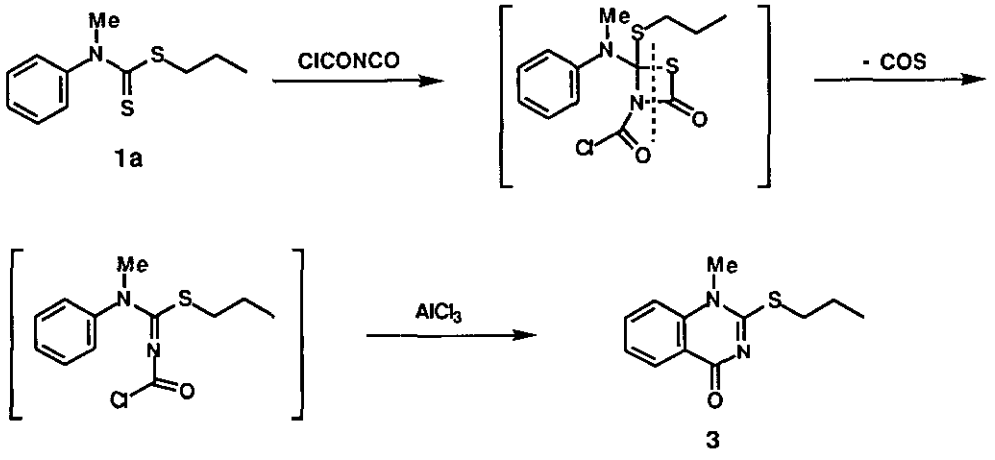


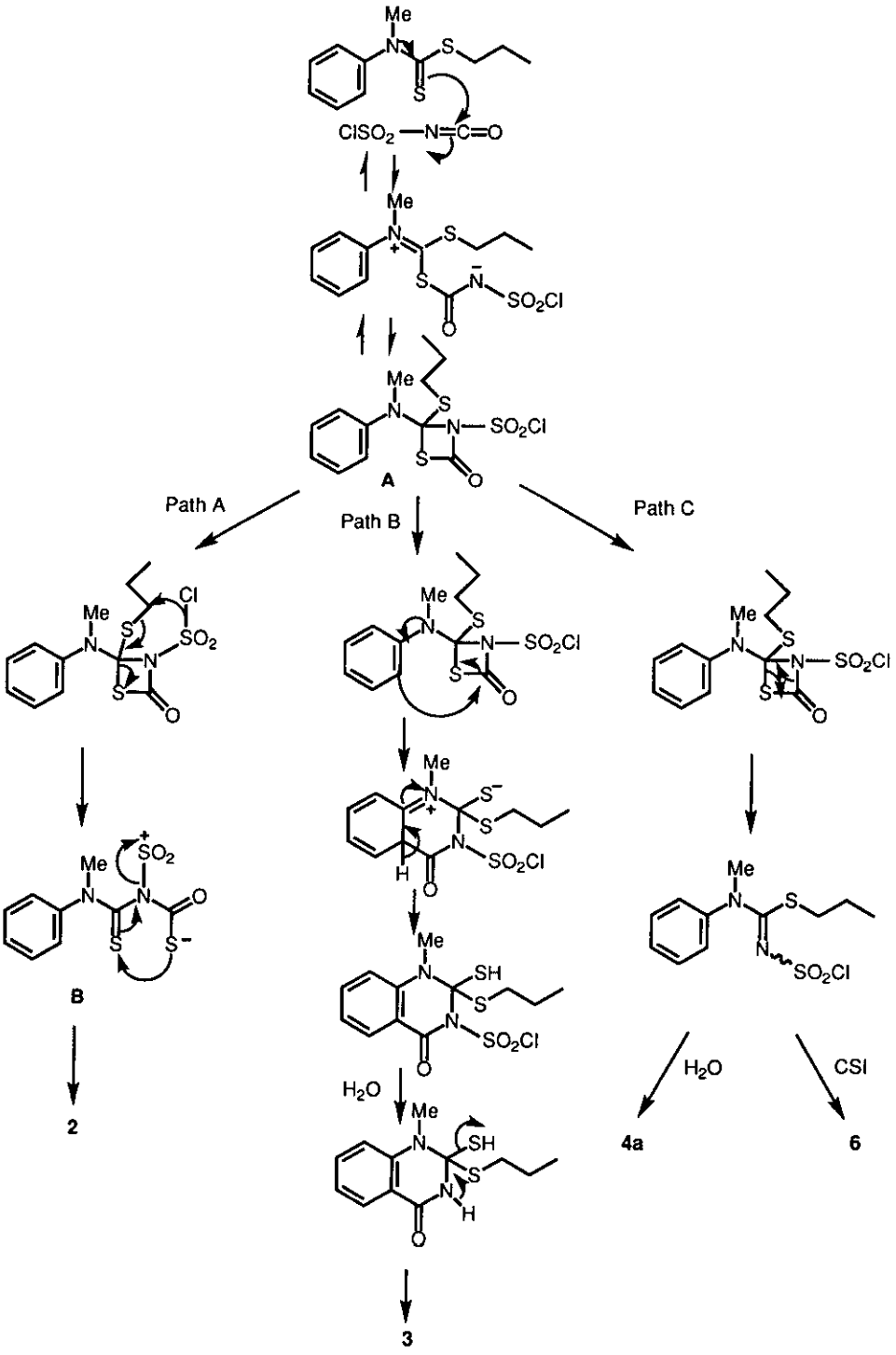
Figure 1



Scheme 2

Interestingly, **2** was not formed in this procedure. Also, **4a** was identical with the product obtained by the reaction of *N*-methyl-*N*-phenylcarbamoyl chloride with sodium propylthiolate. A possible reaction mechanism for the formation of these compounds is shown in Scheme 3.

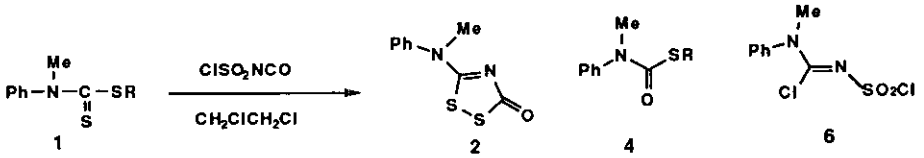
The reaction forming the 1,2,4-dithiazole skeleton is thought to proceed *via* intermolecular [2+2] cycloaddition of dithiocarbamate to CSI to give intermediate (**A**). The chlorine atom of the chlorosulfonyl group then undergoes nucleophilic attack toward the carbon atom of the propyl group



Scheme 3

on a sulfur atom, followed by cleavage of the four-membered ring to yield intermediate (**B**). The sulfur atom of the thiocarbonyl group is then attacked by sulfide and the following elimination of SO_2 gives compound (**2**).

In order to investigate the influence of $AlCl_3$ and the substituents of dithiocarbamates on the reaction, the reactions of various dithiocarbamates with CSI conducted in the absence of $AlCl_3$ were carried out. For example, to a solution of **1b** in 1,2-dichloroethane, CSI was added in portions at 60°C to obtain **2** (30% yield), along with (*Z*)-*N*-methyl-*N*-phenyl-*N*'-chlorosulfonylcarbamimidoyl chloride (**6**) (16% yield) and *N*-methyl-*N*-phenyl-*S*-*i*-propylthiocarbamate (**4b**) (11% yield). Other examples were summarized in Table 1.



1 2 4 6

Starting material		Conditions		Yield (%)		
Compd No.	R	Temp/ °C	Time/ h	2	4	6
1a	*n*-Pr	60	0.5	22	17	12
1b	*i*-Pr	60	0.5	30	11	16
1c	Benzyl	60	0.5	24	8	17
1b	*i*-Pr	reflux	0.5	23	trace	27
1b	*i*-Pr	0 r.t.	0.5 1.0	16	28	6

Table 1 Reaction of Dithiocarbamates with CSI

The structure of **6** was determined by its spectral data (ir, ^{1}H-nmr, ^{13}C-nmr) and elemental analysis. The configuration of **6** was elucidated by X-ray crystallographic analysis[5] as shown in Figure 2.

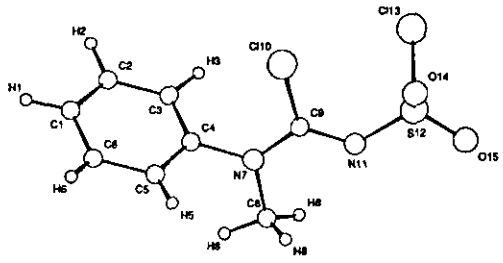


Figure 2

When **1b** was refluxed with CSI, the yield of **6** was brought up to 27%, however, those of **2** and **4b** decreased to 23% and a trace, respectively. When **1b** was stirred at 0°C for 30 min with CSI and then at room temperature for 1 h, the yield of **4b** rose to 28%, while the yields of **2** and **6** decreased to 16 and 6%, respectively.

1,2,4-Dithiazol-3-ones are interesting class of heterocycles with fungicidal activity and potential utility as synthetic intermediates.[6] Two different approaches have been reported for the synthesis of **2**. One method is the reaction of 5-chloro-1,2,4-dithiazol-3-one (**7**) with amine,[7] but sevaral steps are needed to obtain starting material (**7**) and the overall yield is low. The other is the reaction of thiourea with chlorocarbonylsulfenyl chloride [8] which is difficult to obtain. Another useful intermediate for sulfamoylguanidine derivatives is **6**.[9] According to Markovskii's method,[10] dialkylcyanamide is transformed to *N*,*N*-dialkyl-*N'*-chlorosulfonylcarbamimidoyl chloride. However, this method is somewhat troublesome, because the starting material cyanamide is generally prepared by using highly toxic cyanogen bromide.[11]

Our new procedure for the conversion of dithiocarbamate to 5-amino-1,2,4-dithiazol-3-one (**2**) and (*Z*)-*N*,*N*-disubstituted *N'*-chlorosulfonylcarbamimidoyl chloride (**6**) has the following practical merits when compared with previously available methods: 1) the starting material is easy to prepare; 2) CSI is not expensive; 3) the procedure is quite simple as it requires no particular care; and 4) the reaction time is short and the conditions are mild. In summary, the reaction of CSI with dithiocarbamate offers a novel one-step simultaneous synthesis of **2** and **6**.

Biological results

5-Substituted 1,2,4-dithiazol-3-one has been reported to show fungicidal activity,[6] but no specific data are available. Consequently, we evaluated the activity of **2** against a variety of bacterial and fungicidal activities and found it had a minimal growth-inhibitory concentration (MIC) of 25 μg/ml against *Staphylococcus aureus* and *Pasteurella piscicida*. It also exhibited fungicidal activity (500 ppm) against *Botlytis cinerea*.

EXPERIMENTAL

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were determined with a JEOLJNM-GSX 270 spectrometer; chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard, and the coupling constants are in Hz. For column chromatography silica gel (Kiesel gel 60, 70-230 mesh, Merck) was employed.

Reaction of dithiocarbamate with chlorosulfonyl isocyanate (CSI) and $AlCl_3$

CSI (920 mg, 8.0 mmol) was added dropwise with stirring to an ice-cooled solution of propyl *N*-methyl-*N*-phenyldithiocarbamate (1.13 g, 5.0 mmol) in 1,2-dichloroethane (10 ml). The reaction mixture was stirred at 60°C for 30 min, then $AlCl_3$ (870mg, 6.5mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was further stirred at 60°C for 30 min, poured into ice water and extracted with AcOEt. The AcOEt layer was washed, dried over and concentrated. The residue was purified by column chromatography on silica gel using hexane/AcOEt/CH_2Cl_2 (8:1:1 ~ 2:1:1 v/v) as an eluent to give *N*-methyl-*N*-phenyl-*S*-propylthiocarbamate (**4a**) (140mg, 13%), 5-(*N*-methylanilino)-1,2,4-dithiazol-3-one (**2**) (180 mg, 16%), 1-methyl-2-propylthio-4-quinazolinone (**3**) (25 mg, 2%), and 3-propylthio-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5**) (160 mg, 12%).

4a: oil; ir ($CHCl_3$) cm^{-1}: 1650, 1595, 1350, 1275; ^{1}H-nmr ($CDCl_3$) δ: 0.94 (3H, t, J=8 Hz), 1.51-1.67 (2H, m), 2.82 (2H, t, J=7 Hz), 3.33 (3H, s), 7.21-7.48 (5H, m). *Anal.* Calcd for

$C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.82; H, 6.97; N, 6.76.

2: mp 122-123°C (hexane/AcOEt); ir ($CHCl_3$) cm^{-1}: 1690, 1545; ^{1}H-nmr ($CDCl_3$) δ: 3.67 (3H, s), 7.36-7.39 (2H, m), 7.51-7.57 (3H, m); ^{13}C-nmr ($CDCl_3$) δ: 43.52 (q), 126.81 (d,2C), 129.90 (d), 130.20 (d,2C), 140.68 (s), 178.54 (s), 180.04 (s). *Anal.* Calcd for $C_9H_8N_2OS_2$: C, 48.19; H, 3.60; N, 12.49. Found: C, 48.21; H, 3.82; N,12.51.

3: mp 112-114°C (hexane/AcOEt); ir ($CHCl_3$) cm^{-1}: 1640, 1510, 1485, 1375; ^{1}H-nmr ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 1.81 (2H, sext, J=7 Hz), 3.34 (2H, t, J=7 Hz), 3.77 (3H, s), 7.31 (1H, d, J=9 Hz), 7.42 (1H, t, J=7 Hz), 7.70 (1H, ddd, J=9,7,1 Hz), 8.35 (1H, dd, J=7,1 Hz). *Anal.* Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N,11.96. Found: C, 61.81; H, 6.17; N, 11.62.

Synthesis of 1-methyl-2-propyl-4-quinazolinone (3)

N-(Chlorocarbonyl) isocyanate (690 mg, 6.5mmol) was added to a solution of propyl *N*-methyl-*N*-phenyldithiocarbamate (1.13 g, 5.0 mmol) in 1,2-dichloroethane (10 ml). The mixture was stirred at 60°C for 30 min, then $AlCl_3$ (870 mg, 6.5 mmol) and nitromethane (10 ml) were added, and the whole mixture was stirred at 60°C for 25 min, then poured into ice water and extracted with AcOEt. The AcOEt layer was washed, dried over and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt/CH_2Cl_2 (1:1:2 v/v) to give 500 mg (43%) of **3**.

Synthesis of *N*-methyl-*N*-phenyl-*S*-propylthiocarbamate (4a)

To a solution of propylthiol (200 mg, 2.6 mmol) in DMF (5 ml), 60%NaH (120 mg, 3.0mmol) was added with stirring at 0°C. After 10 min, the reaction mixture was stirred for another 10 min at room temperature, then *N*-methyl-*N*-phenylcarbamoyl chloride (440 mg, 2.6 mmol) was added and the whole mixture was stirred at room temperature for 30 min, poured into ice water and extracted with Et_2O. The Et_2O layer was washed, dried over and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (3:1 v/v) to give 290 mg (50%) of **4a**.

***(Z)-N*-Methyl-*N*-phenyl-*N'*-chlorosulfonylcarbamimidoyl chloride (6)**

mp 118-119°C (hexane/AcOEt); ir ($CHCl_3$) cm^{-1}: 1550, 1410, 1385, 1365, 1170; ^{1}H-nmr ($CDCl_3$) δ: 3.60 (3H, s), 7.30-7.32 (2H, m), 7.45-7.58 (3H, m); ^{13}C-nmr ($CDCl_3$) δ: 43.54 (q), 114.75 (s), 125.03 (d), 126.20 (d), 129.77 (d), 130.20 (d), 141.72 (s), 151.66 (s). *Anal.* Calcd for $C_8H_8Cl_2N_2O_2S$: C, 36.09 ; H, 3.09 ; N, 10.53 ; S, 12.03. Found: C, 36.29; H, 3.16; N, 10.44 ; S, 11.62.

ACKNOWLEDGEMENT

We wish to express our thanks to Dr. Reiji Takeda, Director of the Aburahi Laboratories of Shionogi & Co., Ltd., for his encouragement and permission to publish this work.

REFERENCES AND NOTES

1. For part 5, see T. Iwakawa, H. Tamura, M. Masuko, A. Murabayashi, and Y. Hayase, *J. Pesticide Sci.* 1992, **17**, 131.
2. T. Iwakawa, H. Tamura, T. Sato, and Y. Hayase, *Chem. Pharm. Bull.*, 1988, **36**, 4755.
3. T. Iwakawa, H. Tamura, and Y. Hayase, *Chem Pharm. Bull* , 1990, **38**, 1075.
   T. Iwakawa, H. Tamura, A. Murabayashi, and Y. Hayase, *Chem. Pharm. Bull.*, 1991, **39**, 1939.
4. Crystal data: $C_9H_8N_2OS_2$, M_r = 224.3, monoclinic, $P2_1/c$,a = 8.921(1), b = 9.298(2), c = 13.089(2)Å, β = 109.06(1), V = 1022.2(3)Å^3, Z = 4, D_c = 1.457gcm^{-3}, CuKα radiation, λ = 1.54178Å, μ = 4.29mm^{-1}, F(000) = 464. Detailed atomic coordinates, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.
5. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

6. Kurarey Co., Ltd., Jpn. Kokai Tokkyo Koho, 80102506 [*Chem. Abstr.*, 1980, **93**, 232703e]; Kurarey Co., Ltd., Jpn. Kokai Tokkyo Koho, 80118478 [*Chem. Abstr.*, 1981, **94**, 192344a]; Nippon Soda Co., Ltd., Jpn. Kokai Tokkyo Koho, 87195365 [*Chem. Abstr.*, 1988, **108**, 112243m].
7. G. Dahms, A. Haas, and W. Klug, *Chem. Ber.*, 1971, **104**, 2732.
8. J. Goerdeler and K.Nandi, *Chem. Ber.*, 1981, **114**, 549.
9. H. Schroder, E. Fischer, M. Michalik, and G. Oehme, *J. Pract. Chem.*, 1988, **330**, 900.
10. L. N. Markovskii, Yu. G. Shermolovich, and V. I. Shevchenko, *J. Org. Chem. USSR*, 1974, **10**, 492.
11. H.W.J. Cressman, *Org. Synth.*, Coll. Vol., **3**, 1955, 608.

Received, 2nd December, 1993