Synthesis and Properties of 3-Aminoacrylonitriles

Shoji KAJIGAESHI, Kohji MORINO**, Katsuya FUJII***
Shizuo FUJISAKI*, Akiko NISHIDA*
Takashi KOBAYASHI**** and Michihiko NOGUCHI*

(Received July 15, 1991)

Abstract

3-Aminoacrylonitriles, enamines, were obtained from the reaction of 3-methoxyacrylonitrile with aliphatic amines in appropriate solvent, in sealed tube in the presence of aqueous sodium hydroxide, or under reflux, in satisfactory yields. The reactions of 3-aminoacrylonitriles with isocyanates or isothiocyanates gave 3-amino-2-cyanoacrylamides or 3-amino-2-cyanoacrylthioamides, respectively.

1. Introduction

Since 3-aminoacrylonitriles (**1**) are important intermediate for the synthesis of biologically active substances, several procedures for the syntheses of **1** have already been offered in the literature, particularly in the patent. For example, **1** have been obtained from the reaction of 3-chloroacrylonitrile with aliphatic amines (**2**),[1)2)] cyanoacetylene with **2**,[3)4)] and sodium alkoxide of 3-hydroxyacrylonitrile with **2**.[5)] Condensation of *N*, *N*-dimethylformamide acetal with acetonitrile, and catalytic dehydrogenation of 3-(dimethylamino)propanenitrile gave same **1**.[6)7)] Cleavage of 1-alkyl- or 1-arylpyrazoles with sodium amide[8)] or under UV irradiation[9)] gave also 1. Furthermore, plasmolysis of **2** gave **1** with 2-aminoacetonitrile and 3-aminopropiononitrile.[10)]

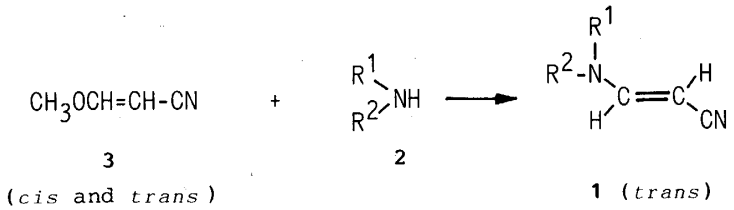
Incidentally, it was already described in some patents that the amination of 3-alkoxyacrylonitriles, which are prepared from sodium alkoxide of 3-hydroxyacrylonitrile with alkyl halide, with **2** gave **1**.[11)12)] In this paper, we wish to report on the syntheses of **1** by the reaction of 3-methoxyacrylonitrile (**3**) with **2** in more detail, and some chemical properties of obtained **1**.

2. Results and Discussion

2.1. Sytheses of 3-Aminoacrylonitriles (1)

The reactions of **3** (mixture of *cis* and *trans* isomers) with **2** in appropriate solvent in sealed tube in the presence of aq. NaOH, or under reflux for many hours gave **1** in satisfactory yields. The results are summarized in Table 1. Attempts to prepare the

*Department of Applied Chemistry and Chemical Engineering
**Kansai Paint Co.
***Terumo Co.
****Ube Laboratory, Ube Industries, Ltd.



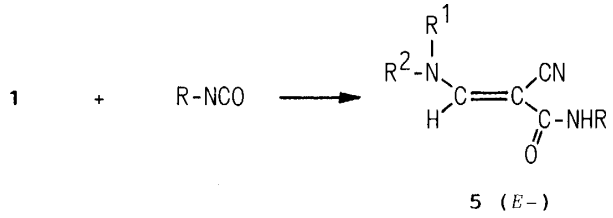
Scheme 1

products **1i**, **1k** and **1n** were unsuccessful.

Geometry of **1** was confirmed as *trans* by ^{1}H NMR measurements. That is, the coupling constants between two ethylene protons showed J= 13-15 Hz, and the chemical shifts of these protons appeared in relatively lower region (e.g., δ values of geminal proton for the amino group: δ= 6.8-7.1 ppm; see Experimental) (Tobey-Simon rule). It can be considered that the reaction passes may be controlled to lead the thermodynamically stable *trans* form.

2.2. Reactions of 1 with Isocyanates

Because the reactions of **1** with heterocumulene as yet are hardly known in the literature, first we choiced isocyanates (**4**) as heterocumulene. Thus, the reactions of **1**



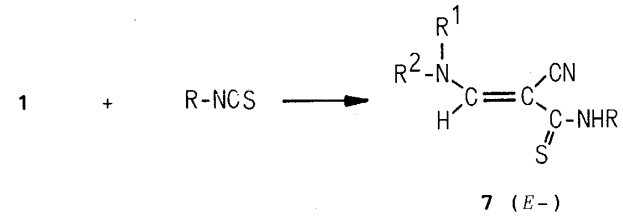
Scheme 2

with **4** in benzene under reflux gave *N*-substituted 3-amino-2-cyanoacrylamide derivatives (**5**). The results are summarized in Table 2.

We confirmed the geometry of **5** as *E*-form by their ^{1}H NMR behavior. That is, the chemical shifts of ethylene proton appeared in lower region (δ=7.5-8.3 ppm; see Experimental) (Tobey-Simon rule).

2.3. Rections of 1 with Isothiocyanates

The reactions of **1** with isothiocyanates (**6**) in benzene or toluene under reflux gave *N*-substituted 3-amino-2-cyanoacrylthioamide derivatives (**7**). The results are summarized in Table 3. The chemical shifts of ethylene proton appeared in lower region (δ= 8-9 ppm; see Experimental). Thus, according to Tobey-Simon rule, we confirmed the geometry of **7** as *E*-form.



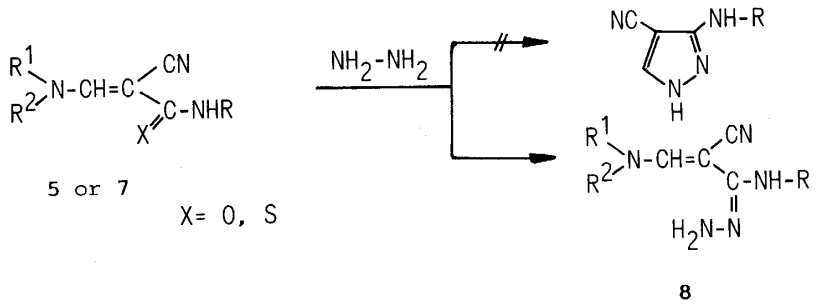
Scheme 3

2.4. Attempted Cycloadditions of 1 with 1,3-Dipoles

Attempts to prepare some heterocyclic compounds from **1** with 1,3-dipoles such as nitron, nitrile-ylide, nitrile-imine, and azomethine-ylide in appropriate solvents were unsuccessful.

2.5. Attempts to Prepare Pyrazole Derivatives from 5 or 7 with Hydrazine

We had tried to prepare pyrazole derivatives having cyano group from **5** (or **7**) with hydrazine. However, only hydrazones of **5** (or **7**) were obtained.



Scheme 4

3. Experimental

All the melting points are uncorrected. ^{1}H NMR spectra were recorded on a JEOL-MH-100 spectrometer. The IR spectra were measured on a JASCO IRA-1 spectrometer.

3.1.1. 3-(1-Pyrrolidinyl)acrylonitrile (1q); General Procedure under Reflux Conditions

To a solution of 3-methoxyacrylonitrile (**3**) (8.30g, 0.1mol) in methanol (50ml) was

Table 1 Syntheses of 3-Aminoacrylonitriles R^1R^2N-CH=CH-CN (1)

	Product 1		Reaction conditions		Solvent (Additive)	Yield[a] (%)	Mp (℃) or Bp(℃/mm Hg)	Literature
	R^1	R^2	Time/h	Temp/℃				
1a	CH_3	H	48	100[b]	CH_3OH	85	103-105/4	3), 5), 9), 11)
1b	C_2H_5	H	24	65[b]	H_2O	99	92-94/5	3)
1c	CH_3	CH_3	16	rt	H_2O/Ether	83	98-100/6.5	6), 15)
1d	C_2H_5	C_2H_5	84	150[b]	Dioxane (aq NaOH)	99	102-104/4	1), 3), 10), 12)
1e	C_3H_7	H	84	150[b]	Dioxane (aq NaOH)	65	95-97/6	—
1f	iso-C_3H_7	H	26	150[b]	Dioxane (aq NaOH)	78	80/6	13)
1g	C_4H_9	H	72	150[b]	Dioxane (aq NaOH)	83	114-116/6.5	3), 14)
1h	*s*-C_4H_9	H	72	150[b]	Dioxane (aq NaOH)	84	108-110/8.5	—
1i	*t*-C_4H_9	H	70	150[b]	Dioxane (aq NaOH)	—	—	15)
1j	*iso*-C_4H_9	H	70	150[b]	Dioxane (aq NaOH)	75	85-87/6	—
1k		H	26	90[b]	Dioxane	—	—	—
1l		H	72	150[b]	Dioxane (aq NoOH)	68	109-111/4	—
1m		H	49	reflux	CH_3OH	63	113-115	5), 11), 12)
1n			24	reflux	Dioxane (aq NaOH)	—	—	—
1o		H	48	reflux	Dioxane	80	79-81	—
1p	$C_6H_5CH_2$	H	62	reflux	C_6H_5-CH_3	81	64-65	5), 11), 12)
1q			48	reflux	CH_3OH	73	52-54	—
1r			86	reflux	CH_3OH	86	55-57	—
1s			25	reflux	C_6H_5-CH_3	81	55-57	—

a) Yield of isolated product.

b) Reaction was carried out in sealed tube.

Table 2 Reaction of **1** with Isocyanates

	Product **5**			Reactuon conditions		Solvent	Yield[a] (%)	Mp (℃)
	R^1	R^2	R	Time/h	Temp/℃			
5a			*p*-Cl-C_6H_4	48	reflux	benzene	41	207-208
5b			*p*-Me-C_6H_4-SO_2	few min.	rt	benzene	87	183-185
5c			C_6H_5	104	reflux	benzene	27	194-195
5d			α-naphthyl	96	reflux	benzene	8	147-148
5e			*p*-Cl-C_6H_4	137	reflux	benzene	26	186-187
5f		H	*p*-Cl-C_6H_4	48	reflux	benzene	70	178-180
5g	$C_6H_5CH_2$	H	*p*-Cl-C_6H_4	50	reflux	benzene	16	174-175

a) Yield of isolated product.

Table 3 Reaction of **1** with Isothiocyanates

	Product **7**			Reactuon conditions		Solvent	Yield[a] (%)	Mp (℃)
	R^1	R^2	R	Time/h	Temp/℃			
7a			*p*-NC-C_6H_4	55	reflux	benzene	41	208-211
7b			*p*-Me-$C_6H_4SO_2$	few min.	rt	benzene	84	178-179
7c			C_6H_5	120	reflux	toluene	43	178-179
7d			CH_3	240	reflux	toluene	17	152-153
7e			*p*-NC-C_6H_4	120	reflux	benzene	36	202-203
7f		H	*p*-NC-C_6H_4	120	reflux	benzene	62	186-187
7g	$C_6H_5CH_2$	H	*p*-NC-C_6H_4	48	reflux	toluene	42	141-142

a) Yield of isolated product.

added pyrrolidine (8.52g, 0.12mol), and the mixture was refluxed for 48 h. After the reaction mixture was allowed to stand at room temperature, precipitated crystals were filtered, washed with cold petroleum benzine to give **1q** as brown plates; yield 8.9 g (73%); mp 52-54 ℃. IR (KBr): 2190 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 1.80-2.34 (4H, m, β-pyrrolidinyl methylene), 2.97-3.42 (4H, m, α-pyrrolidinyl methylene), 3.39 (1H, d, =CH-CN), 7.08 (1H, d, N-CH=).

3.1.2. 3-Cycloheptylaminoacrylonitrile (1o)

Brown plates; IR (KBr): 2185 (CN), 1640 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ= 1.09-2.28 (12H, m, cycloheptyl methylene), 2.95-3.44 (1H, m, CH), 3.66 (1H, d, J= 15 Hz, =CH-CN), 4.60-5.14 (1H, m, NH), 6.67 (1H, dd, J= 8 and 15 Hz, N-CH=).

3.1.3. 3-Morpholinoacrylonitrile (1r)

Brown plates; IR (KBr): 2185 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 3.00-3.27 (4H, m, β-morpholino methylene), 3.51-3.75 (4H, m, α-morpholino methylene), 3.87 (1H, d, =CH-CN), 6.77 (1H, d, N-CH=).

3.1.4. 3-Piperidinoacrylonitrile (1s)

Orange needles; IR (KBr): 2190 (CN), 1620 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ= 1.38-2.80 (6H, m, β- and γ-piperidino methylene), 2.84-3.22 (4H, m, α-piperidino methylene), 3.80 (1H, d, J= 13 Hz, =CH-CN), 6.76 (1H, d, J= 13 Hz, N-CH=).

3.1.5. 3-Cyclopentylaminoacrylonitrile (1l); General Procedure in Sealed Tube

A mixture of aqueous NaOH (0.05g; H_2O 0.5ml), dioxane (5ml), **3** (1.66g, 0.02mol), and cyclopentylamine (5.10g, 0.06mol) was heated in autoclave at 150 ℃ for 3 days. The reaction mixture was concentrated, and was dissolved in choroform (10ml). The chloroform solution was dried over $MgSO_4$, filtered and was concentrated in vacuo. The obtained residue was distilled under reduced pressure to give **1l** as light yellow oil; yield 1.85g (68%); bp 109-112 ℃/4 mmHg. IR (neat): 2245 (CN), 1680 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ= 1.05-2.23 (8H, m, cyclopentyl methylene), 3.30-3.75 (1H, m, CH), 3.75 (1H, d, J= 14 Hz, =CH-CN),4.62-5.41 (1H, m, NH), 6.73 (1H, dd, J= 8 and 14 Hz, N-CH=).

3.1.6. 3-Propylaminoacrylonitrile (1e)

Colorless oil; IR (neat): 2180 (CN), 1640 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ= 0.60-1.28 (3H, m, CH_3), 1.28-2.04 (2H, m, CH_3CH_2), 2.75-3.20 (2H, m, CH_2-N), 3.85 (1H, d, J= 13 Hz, =CH-CN), 4.64-5,40 (1H, m, NH), 6.85 (1H, dd, J= 9 and 13 Hz, N-CH=).

3.1.7. 3-sec-Butylaminoacrylonitrile (1h)

Light yellow oil; IR (neat): 2190 (CN), 1640 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ = 0.76-1.82 (8H, m, CH_3 and C_2H_5), 2.96-3.40 (1H, m, CH), 3.84 (1H, d, J= 14 Hz, =CH-CN), 4.54-5.36 (1H, br., NH), 6.80 (1H, dd, J= 8 and 14 Hz, N-CH=).

3.1.8. 3-*iso*-Butylaminoacrylonitrile (1j)

Light yellow oil; IR (neat): 2185 (CN), 1620 cm^{-1}(C=C); ^1H NMR ($CDCl_3$) δ = 0.84-1.

32 (6H, br.d, $2CH_3$), 1.48-2.12 (1H, m, CH), 2.62-3.43 (2H, m, CH_2), 3.84 (1H, d, J= 15 Hz, =CH-CN), 5.04-5.60 (1H, m, NH), 6.84 (1H, dd, J= 8 and 15 Hz, N-CH=).

3.2.1. N-(p-Chlorophenyl)-2-cyano-3-(1-pyrrolidinyl)acrylamide (5a): General Procedure

To a solution of 1q (0.37 g, 0.003 mol) in dry benzene (10ml) was added *p*-chlorophenylisocyanate (0.46g, 0.003ml), and the mixture was refluxed for 48 h. After the reaction mixture was concentrated in vacuo, obtained precipitate was filtered and recrystallized from ethanol to give **5a**; yield 0.34 g (41%); mp 207-208 ℃. IR (KBr): 2170 (CN), 1655 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 1.56-2.49 (4H, m, β-pyrrolidinyl methylene), 3.51-4.17 (4H, m, α- pyrrolidinyl methylene), 7.17-7.65 (4H, m, aromatic protons), 7.62 (1H, br.s, NH), 8.01 (1H, s, CH=).

3.2.2. 2-Cyano-3-(1-pyrrolidinyl)-N-tosylacrylamide (5b)

Colorless plates; IR (KBr): 2180 (CN), 1680 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 1.68-2.28 (4H, m, β-pyrrolidinyl methylene), 2.40 (3H, s, CH_3), 3.45-4.11 (4H, α-pyrrolidinyl methylene), 7.35, 7.98 (4H, two d, aromatic protons), 7.92 (1H, s, NH), 8.31 (1H, s, CH=).

3.2.3. 2-Cyano-N-phenyl-3-(1-pyrrolidinyl)acrylamide (5c)

Colorless plates; IR (KBr): 2170 (CN), 1655 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ= 1.65-2.43 (4H, m, β-pyrrolidinyl methylene), 3.48-4.17 (4H, m, α-pyrrolidinyl methylene), 6.93-7.74 (6H, m, aromatic protons and NH), 8.01 (1H, s, CH=).

3.2.4. 2-Cyano-N-(α-naphthyl)-3-(1-pyrrolidinyl)acrylamide (5d)

Colorless plates; IR (KBr): 2175 (CN), 1650 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 1.65-2.31 (4H, m, β-pyrrolidinyl methylene), 3.48-4.14 (4H, m, α-pyrrolidinyl methylene), 7.29-8.28 (9H, m, aromatic protons, NH, and CH=).

3.2.5. N-(p-Chlorophenyl)-2-cyano-3-morpholinoacrylamide (5e)

Colorless plates; IR (KBr): 2175 (CN), 1670 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 3.15-4.47 (8H, m, morpholino methylene), 7.14-7.59 (4H, m, aromatic protons), 7.56 (1H, s, NH), 7.80 (1H, s, CH=).

3.2.6. N-(p-Chlorophenyl)-2-cyano-3-cyclohexylaminoacrylamide (5f)

Coloress needles; IR (KBr): 2205 (CN), 1660 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 1.08-2.43 (10H, m, cyclohexyl methylene), 3.03-3.48 (1H, m, CH), 7.23-8.01 (6H, m, aromatic protons, CH=, and CONH), 8.51-9.01 (1H, m, NH).

3.2.7. 3-Benzylamino-N-(p-chlorophenyl)-2-cyanoacrylamide (5g)

Colorless plates; IR (KBr): 2175 (CN), 1645 cm^{-1}(CO); ^1H NMR ($CDCl_3$) δ= 4.41 (2H, d, CH_2), 7.05-7.65 (11H, m, aromatic protons, CH=, and CONH), 9.61-10.05 (1H, m, NH).

3.3.1. 2-Cyano-N-(p-cyanophenyl)-3-(1-pyrrolidinyl)acrylthioamide (7a); General Procedure

To a solution of 1q (1.22 g, 0.01 mol) in dry benzene (50 ml) was added *p*-

cyanophenylisothiocyanate (1.60 g, 0.01 mol), and the mixture was refluxed for 55 h. After the reaction mixture was concentrated in vacuo, obtained precipitates were filtered and recrystallized from ethanol to give **7a**; yield 1.15 g (41%); mp 208-211 ℃. IR (KBr): 2180 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 1.86-2.43 (4H, m, β-pyrrolidinyl methylene), 3.63-4.14 (4H, m, α-pyrrolidinyl methylene), 7.65, 7.86 (4H, two d, aromatic protons), 8.70-8.94 (1H, br.s, NH), 8.82 (1H, s, CH=).

3.3.2 2-Cyano-3-(1-pyrrolidinyl)-*N*-tosylacrylthioamide (7b)

Yellow plates; IR (KBr): 2165 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 1.53-2.13 (4H, m, β-pyrrolidinyl methylene), 2.39 (3H, s, CH_3), 3.48-3.93 (4H, m, α-pyrrolidinyl methylene), 7.26, 7.68 (4H, two d, aromatic protons), 7.85 (1H, s, NH), 8.16 (1H, s, CH=).

3.3.3. 2-Cyano *N*-phenyl-3-(1-pyrrolidinyl)acrylthioamide (7c)

Yellow needles; IR (KBr): 2170 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 1.86-2.55 (4H, m, β-pyrrolidinyl methylene), 3.63-4.35 (4H, m, α-pyrrolidinyl methylene), 7.29-7.83 (5H, m, aromatic protons), 8.61 (1H, br.s, NH), 8.94 (1H, s, CH=).

3.3.4. 2-Cyano-*N*-methyl-3-(1-pyrrolidinyl)acrylthioamide (7d)

Colorless columns; IR (KBr): 2170 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 1.70-2.49 (4H, m, β-pyrrolidinyl methylene), 3.27 (3H, d, CH_3), 3.60-4.17 (4H, m, α-pyrrolidinyl methylene), 7.11-7.77 (1H, br.s, NH), 8.82 (1H, s, CH=).

3.3.5. 2-Cyano-*N*-(p-cyanophenyl)-3-morpholinoacrylthioamide (7e)

Yellow needles; IR (KBr): 2220, 2170 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 3.48-4.50 (8H, m, morpholino methylene), 7.83 (4H, m, aromatic protons), 8.79 (1H, s, CH=), 8.76-9.15 (1H, br.s, NH).

3.3.6. 2-Cyano-*N*-(p-cyanophenyl)-3-cyclohexylaminoacrylthioamide (7f)

Yellow columns; IR (KBr): 2215, 2175 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 0.98-2.80 (10H, m, cyclohexyl methylene), 3.03-3.65 (1H, m, CH), 7.46 (1H, d, CH=), 7.59-8.07 (4H, m, aromatic protons), 8.63 (1H, s, CSNH), 11.93-12.38 (1H, m, NH).

3.3.7. 3-Benzylamino-2-cyano-*N*-(p-cyanophenyl)acrylthioamide (7g)

Yellow needles; IR (KBr): 2210,2190 cm^{-1}(CN); ^1H NMR ($CDCl_3$) δ= 4.56 (2H, d, CH_2), 7.17-8.13 (10H, m, aromatic protons and CH=), 8.73 (1H, s, CSNH), 11.91-12.45 (1H, m, NH).

References

1) E. J. Frazza and L. Rapoport, *U. S. Patent* 3170948; *Chem. Abstr.*, **62**, 14509b (1965).
2) E. M. Movsumzade, T. I. Rasulbekova, S. M. Movsumzade, and G. M. Mamedov, *Zh. Org. Khim.*, **1983**,1393; *Chem. Abstr.*, **99**, 157806j (1983).
3) M. K. Phibbs and P. A. Sipos, *Can. Patent* 1068301; *Chem. Abstr.*, **93**, 45994p (1980).
4) T. Sasaki, T. Yoshioka, and K. Shoji, *J. Chem. Soc., C*, **1969**, 1086.
5) H. Peeters, U. Prange, and W. Vogt, *Ger. Offen.* 2912343; *Chem. Abstr.*, **94**, 102860p (1981).

6) W. Leimgruber and M. Weigele, *U. S. Patent* 3965141; *Chem. Abstr.*, **85**, 77694s (1976).
7) W. Leimgruber and M. Weigele, *U. S. Patent* 3966791; *Chem. Abstr.*, **85**, 142684s (1976).
8) I. I. Grandberg and N. I. Bobrova, *Khim. Geterotsikl, Soedin., Akad. Nauk Latv. SSR,* **1965**, 566; *Chem. Abstr.*, **64**, 3516 (1966).
9) S. Wakamatsu, J. A. Barltrop, and A. C. Day, *Chem. Lett.*, **1982**, 667.
10) B. Fixari, P. Caubere, and M. Felden, *Tetrahedron Lett.*, **1977**, 3067.
11) H. Peeters, U. Prange, and W. Vogt, *Ger. Offen.* 2912344; *Chem. Abstr.*, **94**, 65141g (1981).
12) H. Peeters, U. Prange, and W. Vogt, *Jpn. Kokai Tokkyo Koho*, 80130950; *Chem. Abstr.*, **94**, 102861q (1981).
13) D. Bellus, *Helv. Chim. Acta*, **60**, 2379 (1977).
14) W.Broeckx, N. Overbergh, C. Samyn, G. Smets, and G. L'Abbe, *Tetrahedron*, **27**, 3527 (1971).
15) R. G. Kostyanovsky, A. P. Pleshkova, V. N. Voznesensky, and Yu. I. El'natanov, Org. Mass Spectrum, **15**, 397 (1980); *Chem. Abstr.*, **95**, 60747v (1981).