

Substituent and Solvent Effects on the Tautomeric Equilibria of *N*-Substituted α -(Aminomethylene)purine-6-acetonitrile Derivatives

Norimitsu HAMAMICHI^{*,1)} and Tadashi MIYASAKA^{*}

School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan. Received May 14, 1990

Substituent and solvent effects on the tautomeric equilibration (*E/Z*) of α -(*N*-alkyl and -arylamino)methylene)-9-(methoxymethyl)-9*H*-purine-6-acetonitriles (3a—q) have been studied by means of proton nuclear magnetic resonance spectroscopy in protic and aprotic solvents at 25°C. In chloroform-*d* these compounds (3a—q) exist mainly as the *E*-form. On the other hand, in methanol-*d*₄ or dimethylsulfoxide-*d*₆ the alkylamines (3a—c), phenylamine (3e), *meta*- or *para*-substituted phenylamines (3f—j) and 2,6-disubstituted phenylamines (3p and q) exist mainly as the *Z*-form, while the trityl compound (3d), and *ortho*-substituted compounds (3k—o) showed a predominance of the *E*-form.

Keywords tautomeric equilibrium; substituent effect; solvent effect; hydrogen bonding; α -(aminomethylene)purine-6-acetonitrile

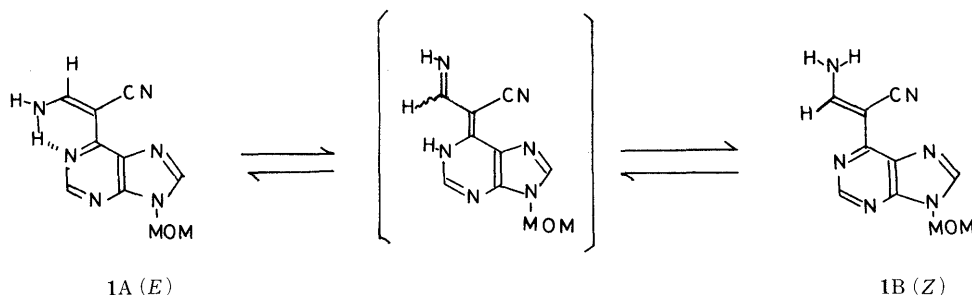
Enamino-acetic acid derivatives are versatile starting materials for the synthesis of heterocyclic compounds²⁾ and also exhibit an interesting tautomeric equilibrium.³⁾ However, the synthesis and tautomerism of β -aminovinyl-substituted heterocycles such as ethyl 3-amino-2-(2-quinolyl)crotonate,⁴⁾ 6-(β -dimethylaminovinyl)pyrimidine⁵⁾ and 2-[2-(aryl amino)vinyl]pyridine derivatives⁶⁾ have rarely been described. Also, investigations of the substituent and solvent effects on the tautomeric equilibrium (*E/Z*) of such systems have not hitherto been described in detail.

In the course of our recent studies on 6-*C*-substituted purine derivatives,⁷⁾ we have reported the synthesis of the α -(aminomethylene)-9-(methoxymethyl)-9*H*-purine-6-acetonitriles (**1**), and we showed that the compound exists as an equilibrium mixture of the enamino-nitrile isomers with *E*- and *Z*-configurations (**1A** and **1B**) rather than in an imino-nitrile equilibrium (Chart 1).⁸⁾ The structure was established by carbon-13 nuclear magnetic resonance (¹³C-NMR) spectroscopy⁹⁾ and proton nuclear magnetic resonance (¹H-NMR) spectroscopy¹⁰⁾ in dimethylsulfoxide-*d*₆ (DMSO-*d*₆). Conversely the geometrical isomer of the enamine moiety of α -(*N,N*-dialkylaminomethylene)-9-(methoxymethyl)-9*H*-purine-6-acetonitriles was found in the *Z*-form only.^{7b)} In this report, we describe the substituent and solvent effects on the tautomeric equilibrium (*E/Z*) of the alkyl- and aryl-substituted α -(aminomethylene)-9-(methoxymethyl)-9*H*-purine-6-acetonitriles (**3a—q**) in chloroform-*d* (CDCl₃), methanol-*d*₄ (CD₃OD), and DMSO-*d*₆.

Results and Discussion

All of the compounds described (**3a—q**) exist mainly as the *E*-form in CDCl_3 solution. This form is stabilized by an intramolecular hydrogen bonding between the amino group of the enamine moiety and *N*-1 of the purine ring. The percent ratios of *E* and *Z* at equilibrium are summarized in Tables I, II and III. The chemical shifts of the vinyl protons and amino protons of the *E* and *Z* isomers of **3a—q** are also shown. In CD_3OD or $\text{DMSO}-d_6$, the *Z*-form ratios of the compounds substituted with alkyl (**3a—c**), phenyl, and *meta*- or *para*-substituted phenyl groups (**3e—j**) increase (Fig. 1, Table I). Accordingly, it was assumed that the increase in the percentage of the *Z*-form in polar solvents is associated with stabilization by the formation of a strong intermolecular hydrogen bonding¹¹⁾ between the amino group of the enamine moiety and the oxygen of the solvent. The increased formation of *Z*-form in $\text{DMSO}-d_6$ over CD_3OD presumably reflected the relative hydrogen bond-accepting ability.¹²⁾

On the contrary, in the cases of the trityl compound (**3d**) and *ortho*-substituted phenyl compounds (**3k—o**) in Table II the *E*-form is predominant in CD₃OD or DMSO-*d*₆ solution. It is noteworthy that the increase in the percentage of the *E*-form is affected by the *ortho*-substituent on the phenyl moiety. Figure 2 shows the possible conformational isomers of the *ortho*-substituted phenyl compound. As the conformers C and D show steric hindrance about the *ortho*-substituent and the vinyl proton, on the basis of Dreiding models, only conformers A and B are expected to



MOM = CH₂OMe

Chart 1

TABLE I. Percent Ratios and ^1H -NMR Signals (δ)^{a)} of C=CH and NH of *E/Z* Forms of **3a–j**.

Compd. No.	R ¹	Ratio (<i>E</i> : <i>Z</i>)	Solvent ^{b)}	C=CH		NH	
				<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>
3a	Me	80:20	C	7.47 (d)	9.33 (d)	10.98 (m)	6.22 (m)
		40:60	M	7.76 (s)	9.22 (s)		
		24:76	D	7.76 (d)	9.22 (m)	10.92 (m)	8.32 (s)
3b	CH ₂ Ph	81:19	C	7.51 (d)	9.54 (d)	11.45 (m)	6.46 (m)
		42:58	M	7.39 (s)	9.42 (s)		
		30:70	D	8.00 (d)	9.33 (brs)	11.43 (m)	^{c)}
3c	C(Me) ₃	24:76	C	7.57 (d)	9.51 (d)	11.45 (d)	^{c)}
		47:53	M	7.79 (s)	9.69 (s)		
		32:68	D	7.88 (d)	9.58 (d)	11.66 (d)	8.52 (m)
3d	C(Ph) ₃	100:0	C	7.29 (m)		12.49 (d)	
		87:13	M	7.41 (m)	9.69 (s)		
		83:17	D	7.37 (m)	9.33 (m)	13.11 (d)	^{c)}
3e	Ph	84:16	C	8.00 (d)	9.95 (d)	13.19 (d)	^{c)}
		41:59	M	8.31 (s)	10.02 (s)		
		18:82	D	8.49 (d)	9.89 (brs)	13.45 (d)	10.73 (s)
3f	<i>p</i> -MePh	73:27	C	7.97 (d)	13.14 (d)	9.86 (d)	^{c)}
		44:56	M	8.26 (s)	9.98 (s)		
		20:80	D	8.43 (d)	9.86 (s)	13.41 (d)	10.59 (s)
3g	<i>p</i> -MeOPh	88:12	C	7.90 (d)	9.83 (d)	13.26 (d)	^{c)}
		42:58	M	8.17 (s)	9.90 (s)		
		19:81	D	8.38 (d)	9.79 (s)	13.38 (d)	10.60 (s)
3h	<i>p</i> -BrPh	83:17	C	7.94 (d)	9.98 (d)	13.22 (d)	^{c)}
		^{d), d)}	M				
		20:80	D	8.48 (d)	9.83 (brs)	13.44 (d)	10.72 (s)
3i	<i>m</i> -MePh	88:12	C	8.00 (d)	9.88 (d)	13.13 (d)	^{c)}
		44:56	M	8.28 (s)	9.99 (s)		
		22:78	D	8.47 (d)	9.87 (brs)	13.37 (d)	10.65 (s)
3j	<i>m</i> -MeOPh	68:32	C	7.99 (d)	9.92 (d)	13.15 (d)	
		41:59	M	8.31 (s)	10.02 (s)		
		20:80	D	8.53 (d)	9.89 (brs)	13.41 (d)	9.89 (s)

a) $J = 13$ Hz. b) C, CDCl₃; M, CD₃OD; D, DMSO-*d*₆. c) Ambiguous. d) Values are not given for insoluble samples.

TABLE II. Percent Ratios and ^1H -NMR Signals (δ)^{a)} of C=CH and NH of *E/Z* Forms of **3k–o**.

Compd. No.	R ²	R ³	Ratio (<i>E</i> : <i>Z</i>)	Solvent ^{b)}	C=CH		NH	
					<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>
3k	Me	H	95:5	C	8.06 (d)	^{c)}	13.26 (d)	^{c)}
			^{d), d)}	M				
			71:29	D	8.51 (d)	9.57 (d)	13.40 (d)	^{c)}
3l	MeO	H	94:6	C	8.05 (d)	^{c)}	13.79 (d)	^{c)}
			^{d), d)}	M				
			94:6	D	8.54 (d)	9.29 (d)	13.51 (d)	9.85 (d)
3m	Br	H	^{d), d)}	C				
			^{d), d)}	M				
			86:14	D	8.64 (d)	9.60 (d)	13.43 (d)	^{c)}
3n	Me	Me	93:7	C	8.00 (d)	9.81 (d)	13.27 (d)	^{c)}
			^{d), d)}	M				
			65:35	D	8.65 (d)	9.53 (d)	13.43 (d)	10.00 (s)
3o			94:6	C	8.15 (d)	9.96 (d)	13.87 (d)	^{c)}
			^{d), d)}	M				
			62:38	D	8.63 (d)	9.71 (d)	14.02 (d)	10.78 (m)

a) $J = 13$ Hz. b) C, CDCl₃; M, CD₃OD; D, DMSO-*d*₆. c) Ambiguous. d) Values are not given for insoluble samples.

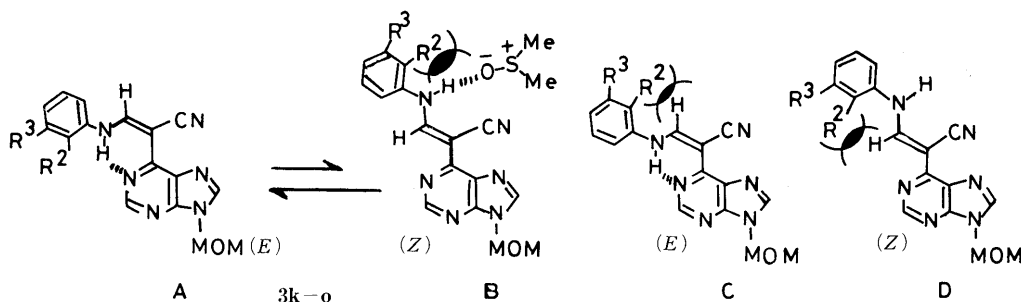


Fig. 2

be stable. Conformer A is more likely to be favored, as conformer B would be destabilized by cleavage of the intermolecular hydrogen bonding between the amino group and the solvent. A similar argument would apply to the trityl compound (**3d**).

The 2,6-disubstituted phenyl compounds (**3p** and **q**) in a polar solvent exist predominantly as the *Z*-form, which is stabilized by an intermolecular hydrogen bonding (Table III). In the ^1H -NMR spectra of **3p** and **3q**, the chemical shifts of the two sets of vinyl protons were shifted upfield by about 0.5 ppm (due to the anisotropic shielding effect of the phenyl ring) compared to those of compounds **3e** and **3f**. Furthermore, these compounds showed a maximum absorption in the ultraviolet (UV) spectra at 347 nm, which is similar to that of **3a** but differs substantially from those of compounds **3e**, **f** and **k** (Table IV). Accordingly, on the basis of these results we conclude that the 2,6-disubstituted phenyl moiety was twisted out of the plane of the enamine moiety. Figure 3 shows the possible conformational isomers for **3p** and **3q**. The conformers C and D are affected

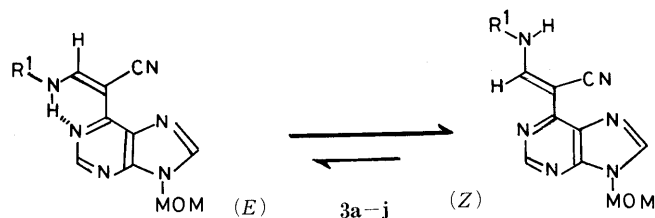


Fig. 1

by the steric repulsion between the two *ortho*-substituents and the amino proton in addition to the vinyl proton. It is therefore implicit that the twisted *ortho*-disubstituted phenyls (A and B) are more favorable, but in polar solvents the twisted B-conformer is predominant due to the formation of an intermolecular hydrogen bonding between the amino group and the DMSO-*d*₆ molecule.

In conclusion, it was found that the compounds substituted with naphthyl, trityl and *ortho*-substituted phenyl groups inhibit intermolecular hydrogen bonding in polar solvents. However, the *tert*-butyl group has no such effect. Also, the inclusion of 2,6-disubstituted phenyl groups

resulted in a complete loss of interannular conjugation due to steric effects, and, in polar solvents, the twisted form is favorable for intermolecular hydrogen bonding. In CDCl₃, the *E*-form is most stable due to interannular conjugation and intramolecular hydrogen bonding. In this case the *N*-substituent does not have any effect on the *E/Z* ratio.

Experimental

All melting points were determined on a Yamato capillary melting point apparatus, MP-21, and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrophotometer. UV spectra were measured using a Hitachi EPS-3T spectrophotometer. ¹H-NMR spectra were recorded on JEOL JNM-FX 100 (99.6 MHz) spectrometers using 3 mg of the sample in 0.4 ml of solvent, with tetramethylsilane as an internal standard. Probe temperature was 25 °C. The *E/Z* ratios of **3a–q** were determined on the basis of the relative peak areas of the vinyl and amine signals of the *E*

TABLE III. Percent Ratios and ¹H-NMR Signals (δ)^a of C=CH and NH of *E/Z* Forms of **3p** and **q**

Compd. No.	R ⁴	Ratio (<i>E/Z</i>)	Sol-vent ^b	C=CH		NH	
				<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>
3p	Me	89:11	C	7.59 (d)	^c	12.66 (d)	9.40 (s)
		38:62	M	7.74 (s)	9.65 (s)		
		17:83	D	7.92 (d)	9.62 (d)	12.88 (d)	9.98 (d)
3q	Et	92:8	C	7.50 (d)	^c	12.60 (d)	9.29 (d)
		37:63	M	7.69 (s)	9.69 (s)		
		15:85	D	7.59 (d)	9.64 (s)	12.82 (d)	10.04 (d)

a) *J* = 13 Hz. b) C, CDCl₃; M, CD₃OD; D, DMSO-*d*₆. c) Ambiguous.

TABLE IV. UV Spectral Data for **3a**, **e**, **f**, **k**, **p**, and **q**

Compd. No.	λ max (MeOH) nm (log ε)
3a	237 (4.14), 259 (3.87, sh), 342 (4.47), 351 (4.45, sh)
3e	241 (4.23), 262 (4.18), 371 (4.59)
3f	241 (4.19), 263 (4.14), 374 (4.52)
3k	241 (4.17), 262 (4.04), 377 (4.49)
3p	237 (4.17), 260 (4.04, sh), 347 (4.47)
3q	236 (4.18), 260 (4.00, sh), 347 (4.47)

TABLE V. Physicochemical and Analytical Data for **3a–q**

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	ν (IR) cm ⁻¹	Formula	Analysis: Calcd (Found)		
					C	H	N
3a	83	197–199 (MeOH–hexane)	2192 (CN)	C ₁₁ H ₁₂ N ₆ O	54.09 (54.38)	4.95 (4.96)	34.41 (34.29)
3b	93	142–150 (MeOH–hexane)	2200 (CN)	C ₁₇ H ₁₆ N ₆ O	63.73 (63.54)	5.04 (4.94)	26.24 (26.53)
3c	91	169–170 (EtOH–hexane)	2196 (CN)	C ₁₄ H ₁₈ N ₆ O	58.73 (59.01)	6.33 (6.23)	29.35 (29.57)
3d	75	192–193 (CHCl ₃ –hexane)	2200 (CN)	C ₂₉ H ₂₄ N ₆ O	73.71 (73.50)	5.11 (5.00)	17.78 (17.50)
3e	94	216–217 (CHCl ₃ –MeOH)	2196 (CN)	C ₁₆ H ₁₄ N ₆ O	62.73 (63.01)	4.61 (4.56)	27.44 (27.30)
3f	91	206–208 (dec.) (CH ₂ Cl ₂ –EtOH)	2200 (CN)	C ₁₇ H ₁₆ N ₆ O	63.73 (63.73)	5.04 (5.00)	26.24 (25.95)
3g	87	194–195 (dec.) (CHCl ₃ –MeOH)	2205 (CN)	C ₁₇ H ₁₆ N ₆ O ₂	60.70 (60.78)	4.80 (4.71)	24.99 (24.94)
3h	91	230–233 (dec.) (DMF–EtOH)	2205 (CN)	C ₁₆ H ₁₃ BrN ₆ O	49.88 (50.14)	3.40 (3.33)	21.81 (22.11)
3i	90	205–206 (dec.) (CHCl ₃ –EtOH)	2195 (CN)	C ₁₇ H ₁₆ N ₆ O	63.73 (63.76)	5.04 (5.12)	26.24 (25.95)
3j	93	167–168 (CHCl ₃ –EtOH)	2190 (CN)	C ₁₇ H ₁₆ N ₆ O ₂	60.70 (60.53)	4.80 (4.66)	24.99 (25.21)
3k	90	251–253 (dec.) (CHCl ₃ –EtOH)	2200 (CN)	C ₁₇ H ₁₆ N ₆ O	63.73 (63.93)	5.04 (4.94)	26.24 (26.10)
3l	93	230–231 (CHCl ₃ –EtOH)	2200 (CN)	C ₁₇ H ₁₆ N ₆ O ₂	60.70 (60.67)	4.80 (4.69)	24.99 (25.29)
3m	82	256–258 (dec.) (DMF–EtOH)	2200 (CN)	C ₁₆ H ₁₃ BrN ₆ O	49.88 (49.97)	3.40 (3.22)	21.81 (21.51)
3n	90	233–234 (dec.) (CHCl ₃ –EtOH)	2205 (CN)	C ₁₈ H ₁₈ N ₆ O	64.65 (64.51)	5.43 (5.40)	25.14 (25.32)
3o	96	218–219 (CH ₂ Cl ₂ –MeOH)	2212 (CN)	C ₂₀ H ₁₆ N ₆ O	67.40 (67.17)	4.53 (4.47)	25.14 (25.18)
3p	91	163–164 (CH ₂ Cl ₂ –EtOH)	2192 (CN)	C ₁₈ H ₁₈ N ₆ O	64.65 (64.95)	5.43 (5.29)	25.14 (25.06)
3q	86	129–130 (CH ₂ Cl ₂ –hexane)	2195 (CN)	C ₂₀ H ₂₂ N ₆ O	66.28 (66.15)	6.11 (6.23)	23.18 (23.18)

DMF: dimethyl formamide.

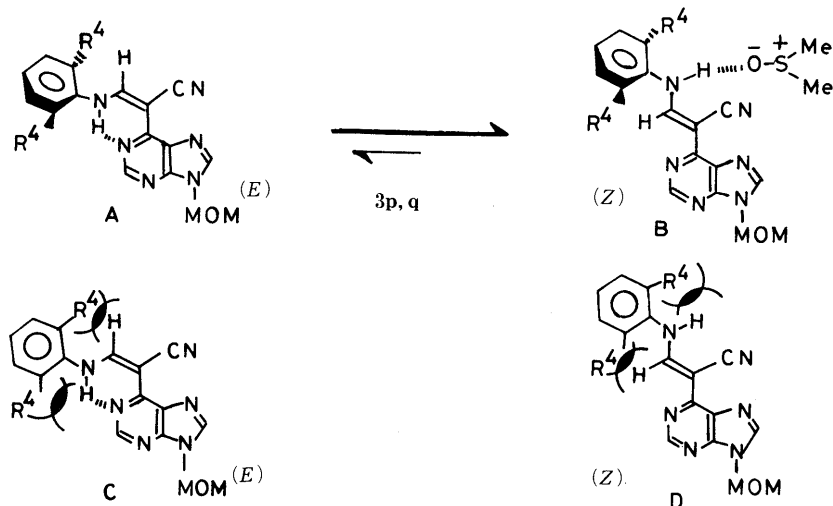


Fig. 3

and Z isomers The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; sh, shoulder; and dd, doublet of doublets.

α -(N-Methylaminomethylene)-9-(methoxymethyl)-9H-purine-6-acetonitrile (3a) A mixture of **1** (0.300 g, 1.30 mmol) and 20% (w/w) ethanolic methylamine (8 ml) was heated in a sealed tube at 80–85°C for 1 h. The reaction mixture was cooled, and the resulting precipitate was collected by filtration, and recrystallized (Table V).

General Procedure for the Preparation of 3b–q A mixture of **1** (1.0 mmol) and an amine (**2b–q**) (3.0 mmol) in ethanol (7 ml) was heated under reflux for 1.5 h with stirring, then allowed to cool. The precipitate was collected by filtration, and recrystallized to give the corresponding product, **3b–q** (see Table V). It should be noted that reaction of **1** with aryl amines required prolonged reaction times of between 2 and 14 d.

References and Notes

- 1) Present address: Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Va 22901, U.S.A.
- 2) a) M. H. Elnagdi, *Heterocycles*, **20**, 519 (1983), and references cited therein; b) V. G. Granik, L. V. Ershov, S. I. Grizik and V. V. Chistyakov, *Chem. Heterocycl. Compd.*, **20**, 1026 (1984); c) A. A. Krauze, É. É. Liepin'sh, Z. A. Kalme, Y. É. Pelcher and G. Y. Dubur, *ibid.*, **20**, 1241 (1984); d) R. J. Linderman and K. S. Kirollos, *Tetrahedron Lett.*, **30**, 6173 (1989).
- 3) a) G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963); b) R. Huisgen, K. Herbig, A. Siegl and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); c) A. G. Sánchez and A. M. Valle, *J. Chem. Soc., Perkin Trans. 2*, **1973**, 15; d) C. Skötsch and E. Breitmaier, *Chem. Ber.*, **113**, 795 (1980); e) A. G. Sanchez and E. Sempere, *J. Chem. Soc., Perkin Trans. 2*, **1981**, 561; f) J. L. Chiara, A. G. Sanchez and F. J. Hidalgo, *ibid.*, **1987**, 301.
- 4) H. Yamanaka, H. Egawa and T. Sakamoto, *Chem. Pharm. Bull.*, **26**, 1291 (1978).
- 5) R. F. Abdulla and R. S. Brinkmeyer, *Tetrahedron*, **35**, 1675 (1979), and references cited therein.
- 6) M. Balogh, I. Hermecz, K. Simon and L. Pusztay, *J. Heterocycl. Chem.*, **26**, 1755 (1989).
- 7) a) N. Hamamichi and T. Miyasaka, *Tetrahedron Lett.*, **26**, 4743 (1985); b) *Idem*, *J. Heterocycl. Chem.*, **27**, 835 (1990); c) *Idem*, *Heterocycles*, **31**, 321 (1990); d) *Idem*, *Chem. Pharm. Bull.*, **38**, 2018 (1990).
- 8) The ^{13}C -NMR signals of the nitrile appeared at δ 116.8 ($^3J_{\text{CN,H}}=11.0$ Hz, Z) (major signal) and at δ 121.2 ($^3J_{\text{CN,H}}=4.9$ Hz, E) (minor signal). Also the ^1H -NMR signals of the vinyl proton appeared at δ 9.28 (dd) due to the Z-form, and at δ 7.71 (dd) due to E-form.
- 9) E. P. Prokofev and E. I. Krapeiskaya, *Tetrahedron Lett.*, **1979**, 737.
- 10) S. Torfimenko, *J. Org. Chem.*, **28**, 2755 (1963).
- 11) V. V. Lapachev, O. A. Zagulyaeva, O. P. Peterenko, S. F. Bychkov, and V. P. Mamaev, *Chem. Heterocycl. Compd.*, **20**, 676 (1984).
- 12) A. R. Miller, *J. Org. Chem.*, **41**, 3599 (1976).