

**SYNTHESES OF 2,4-DIAMINOPYRIMIDINES AND 1-AMINOISOQUINOLINES
IN THE REACTIONS OF ALKYL AND BENZYL KETONES WITH CYANAMIDE
AND *N,N*-DIMETHYLCYANAMIDE**

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Abstract - The reaction of alkyl and benzyl ketones with cyanamide and *N,N*-dimethylcyanamide in the presence of POCl₃ was examined. At the first stage, chloroformamidines were formed. In the presence of TiCl₄, they underwent further reactions to the derivatives of 1-aminoisoquinoline and 2,4-diaminopyrimidine. The effect of a constitution of substrates on adequate ratios of heterocyclic compounds is discussed.

The earlier studies on reactions of benzyl and alkyl ketones in the presence of phosphoryl chloride^{1,2} have proved a possibility to synthesize *N*-vinylimidoyl compounds by the Ritter type reaction.³ These compounds were then used in preparation of isoquinoline, pyrimidine or pyridine derivatives.^{1,2,4} On the other hand, it is known that *N*-vinylimidoyl chlorides easily react with cyanamide⁵ and *N,N*-dimethylcyanamide⁶ yielding 4-aminopyrimidine derivatives.

In this work we have commenced to study the reactions of alkyl and benzyl ketones (**1**) with cyanamide or *N,N*-dimethylcyanamide (**2**) to *N*-vinyl- or *N*-styrylchloroformamidines (**3**) in order to their further use in synthesis of 2,4-diaminopyrimidines (**7**) and 1-aminoisoquinolines (**8**).

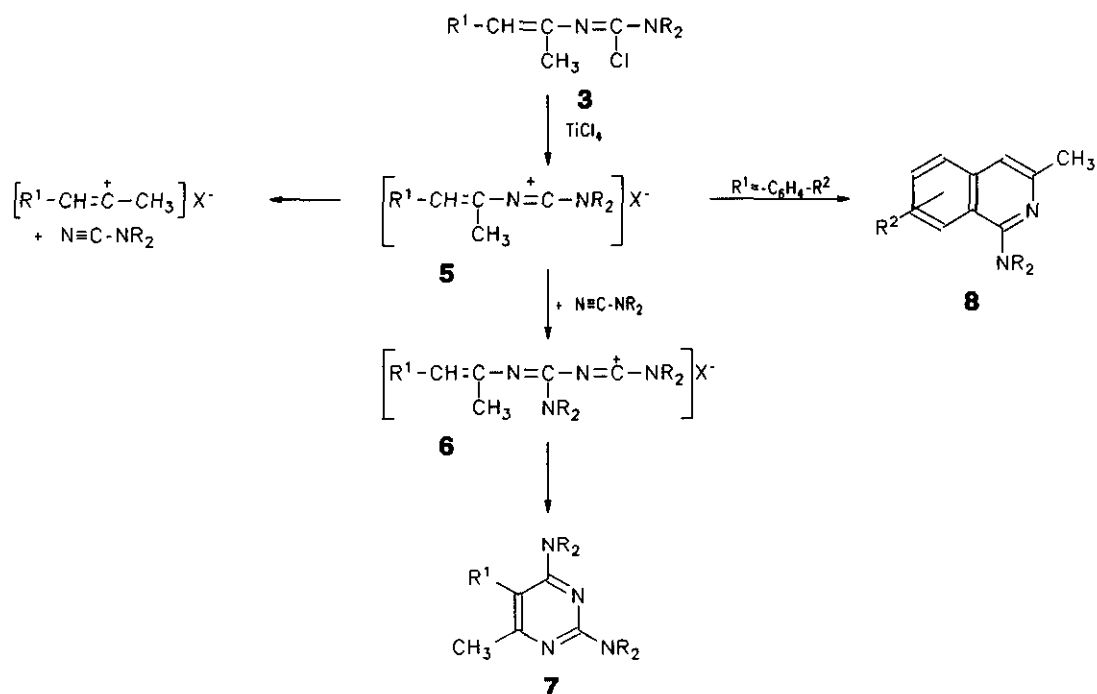
A few examples for the reactions of ketones with cyanamide are only known yielding the corresponding cyanoimines,⁷⁻⁹ compounds obtained from a reaction of the amino group in cyanamide with carbonyl carbon. The reaction of the nitril nitrogen atom in cyanamide and its derivatives with ketones has not been hitherto known.

Examining the reaction of alkyl ketones with cyanamide and its *N,N*-dimethyl derivative in the presence of phosphoryl chloride we have found that adequate chloroformamidines can be prepared provided the nitril nitrogen atom in cyanamide will attack the activated carbonyl carbon atom. It is possible to ensure such a course of reaction only when *O*-phosphorylation of the carbonyl oxygen will take place at the initial

Table 1. Pyrimidines (7) and isoquinolines (8).

R ¹	R	Mol. ratio (1): (2)	Pyrimidines (7)		R ²	Isoquinolines (8)	
			Yield % mol	bp (°C/Torr) or mp (°C)		Yield % mol	bp (°C/Torr) or mp (°C)
a	H	CH ₃	1:2	65	158/31 ^{a)}		
b	CH ₃	CH ₃	1:2	64	140/31		
c	C ₂ H ₅	CH ₃	1:2	61	160/28		
d	(CH ₃) ₂ CH	CH ₃	1:2	60	163/31		
e	C ₆ H ₅	CH ₃	1:2	65	H	-	124/1
		1:1	20			3	104-105
		1:0.7	8			11	
f	3-CH ₃ C ₆ H ₄	CH ₃	1:2	64	6-CH ₃	10	154/4
		1:1	14	220/31		31	72-74
g	4-CH ₃ C ₆ H ₄	CH ₃	1:2	50	7-CH ₃	6	160/13
		1:1	12	88-90		21	36-38
h	3-ClC ₆ H ₄	CH ₃	1:2	58	6-Cl	5	95-97
		1:1	25	68-69		25	
i	4-ClC ₆ H ₄	CH ₃	1:2	55	7-Cl	4	53-55
k	3-CH ₃ OC ₆ H ₄	CH ₃	1:1	-	6-CH ₃ O	48	160/4
l	4-CH ₃ OC ₆ H ₄	CH ₃	1:2	35	7-CH ₃ O	7	173/10
		1:1	9	104-105		33	51-52
m	3-NO ₂ C ₆ H ₄	CH ₃	1:2	71		-	
n	4-NO ₂ C ₆ H ₄	CH ₃	1:2	75		-	
o	C ₆ H ₅	H	1:1	14	H	14	129-130 ^{c)}

^{a)} lit.,¹⁰ bp = 84-85/2^{b)} lit.,¹¹ mp = 249-250^{c)} lit.,¹² mp = 130-131



The yield and ratios of the resulting pyrimidines and isoquinolines are considerably influenced by electron effects on the substituents present in the benzene ring (R^2) and the ratio of the substrates (Table 1). Generally, the electron withdrawing substituents facilitate a formation of pyrimidines, while the electron donating substituents, increasing the electron density in the 2 position of the benzene ring make easily the intramolecular closure of the isoquinoline ring. When a ratio of *N,N*-dimethylcyanamide to benzyl ketones is smaller the reaction is shifted towards isoquinolines. Also, the transition from *N,N*-dimethylcyanamide ($\text{R} = \text{CH}_3$) to cyanamide ($\text{R} = \text{H}$) changes the ratio of the products towards isoquinolines, mainly due to steric hindrance effects.

Among the synthesized heterocyclic compounds, 2,4-bis(dimethylamino)-6-methylpyrimidine,¹⁰ 2,4-diamino-6-methyl-5-phenylpyrimidine¹¹ and 1-amino-3-methylisoquinoline¹² were obtained by other methods.

EXPERIMENTAL

Mass spectral data were performed on a Shimadzu QP-2000 spectrometer. Microanalyses were performed with Perkin-Elmer 240 C analyzer. The physical and spectral data of the compounds are given in Table 1, Table 2 and Table 3.

1,1-Dimethyl-3-(1-methyl-2-phenylvinyl)urea (4e)

A solution of benzyl methyl ketone (13.4 g, 0.1 mol) and POCl_3 (7.6 g, 0.05 mol) in 50 ml of anhydrous benzene was heated under reflux for 10 min. Then, *N,N*-dimethylcyanamide (3.5 g, 0.05 mol) was added. The mixture was left at a room temperature for 2 h. Benzene was removed on a rotary evaporator and the residue was washed with anhydrous ether in order to separate an excess of benzyl methyl ketone. The resulting chloroformamidinium salt in a form of oil was dissolved in a small amount of methanol and gradually poured into 5 % aqueous Na_2CO_3 solution, vigorously agitated. The solution was extracted with chloroform. Having the chloroform removed, the residue was washed with hexane to remove contaminants. A pure compound (**4e**) is obtained as yellowish oil in yield of 6.1 g (60 %). $^1\text{H-Nmr}$ (CDCl_3) δ 2.12 (d, $J = 1.2$ Hz, 3H, CH_3), 2.82 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 5.10 (wide s, 1H, NH), 6.87 (q, $J = 1.2$ Hz, 1H, CH), 7.00-7.40 (m, 5H, C_6H_5). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$: C, 70.55; H, 7.89, N, 13.72. Found: C, 70.30; H, 7.70; N, 13.50.

Derivatives of 2,4-diaminopyrimidine (7) and 1-aminoisoquinoline (8)

A solution of alkyl or benzyl ketone (0.05 mol) and POCl_3 (7.6 g, 0.05 mol) in 50 ml of anhydrous benzene was heated under reflux for 10 to 15 min. Into the cooled solution *N,N*-dimethylcyanamide in quantity according to a molar ratio (Table 1) (7.0 g, 0.1 mol; 3.5 g, 0.05 mol or 2.45 g, 0.035 mol) or cyanamide (2.1 g, 0.05 mol) in 5 ml of anhydrous ether was added dropwise. The mixture was left at a room temperature for 1 h. Next, a solution of TiCl_4 (9.5 g, 0.05 mol) in 20 ml of anhydrous benzene was added dropwise into the reaction mixture with its simultaneous agitation and cooling. The mixture was heated for 1.5 h under reflux condenser, cooled and then 150 ml water was added. The obtained mixture was filtered off and the sediment was washed with ether. The filtrate was alkalized with 20 % NaOH solution and extracted with ether or chloroform. The prepared 2,4-bis(dimethylamino)-5-alkylpyrimidines were purified by distillation, whereas the mixtures of 2,4-diamino-5-phenylpyrimidines and 1-aminoisoquinolines were separated by distillation or fractional crystallization from methanol or hexane. Data of mass spectra and microanalysis of pyrimidines (**7**) and isoquinolines (**8**) were as follows: (**7b**) Ms (m/z): 194 (M^+ , 56.3 %). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{N}_4$: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.71; H, 9.40; N, 28.89. (**7c**) Ms (m/z): 208 (M^+ , 44.4 %). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_4$: C, 63.42; H, 9.68; N, 26.90. Found: C, 63.40; H, 9.72; N, 26.88. (**7d**) Ms (m/z): 222 (M^+ , 27.7 %). Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{N}_4$: C, 64.82; H, 9.97; N, 25.21. Found: C, 65.00; H, 9.94; N, 25.06. (**7e**) Ms (m/z): 256 (M^+ , 100 %). Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_4$: C, 70.28; H, 7.86; N, 21.86. Found: C, 70.09; H, 7.94; N, 21.97. (**7f**) Ms (m/z): 270 (M^+ , 100 %). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_4$: C, 71.07; H, 8.20; N, 20.73. Found: C, 70.98; H, 8.31; N, 20.71. (**7g**) Ms (m/z): 270 (M^+ , 100 %). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_4$: C, 71.07; H, 8.20; N, 20.73. Found: C, 70.93; H, 8.27; N, 20.80. (**7h**) Ms (m/z): 290

Table 2. Spectral data of pyrimidines (7).

Pro- duct	uv (methanol/water) ^{a)} medium ($\lambda_{\max}$ nm) ($\epsilon \cdot 10^{-3}$)	¹ H nmr (δ ppm, chloroform- <i>d</i> ₁ /TMS) ^{b)}
7a	basic 228 (23.0); 298 (8.3)	2.20 (s, 3H, 6-CH ₃); 2.98 (s, 6H, 4-N(CH ₃) ₂); 3.10 (s, 6H, 2-N(CH ₃) ₂); 5.57 (s, 1H, 5-H)
	acidic 229 (26.0); 255 (13.3)	
7b	basic 242 (18.8); 309 (7.5)	2.02 (s, 3H, 5-CH ₃); 2.24 (s, 3H, 6-CH ₃); 2.86 (s, 6H, 4-N(CH ₃) ₂); 3.09 (s, 6H, 2-N(CH ₃) ₂)
	acidic 230 (21.1); 264 (12.4)	
7c	basic 244 (18.6); 311 (7.0)	1.11 (t, J = 7.3 Hz, 3H, CH ₂ -CH ₃); 2.29 (s, 3H, 6-CH ₃); 2.50 (q, J = 7.3 Hz, 2H, CH ₂ -CH ₃); 2.88 (s, 6H, 4-N(CH ₃) ₂); 3.09 (s, 6H, 2-N(CH ₃) ₂)
	acidic 231 (22.7); 266 (12.3)	
7d	basic 243 (18.8); 311 (6.1)	1.25 (d, J = 7 Hz, 6H, (CH ₃) ₂ CH); 2.36 (s, 3H, 6-CH ₃); 2.78 (s, 6H, 4-N(CH ₃) ₂); 3.05 (m, J = 7 Hz, 1H, CH); 3.09 (s, 6H, 2-N(CH ₃) ₂)
	acidic 233 (22.5); 267 (11.6)	
7e	basic 236 (21.4); 308 (7.9)	2.04 (s, 3H, 6-CH ₃); 2.33 (s, 3H, <i>m</i> -CH ₃); 2.66 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 7.03-7.37 (m, 5H _{Arom})
	acidic 234 (30.6)	
7f	basic 237 (25.6); 308 (10.5)	2.05 (s, 3H, 6-CH ₃); 2.66 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 7.00-7.30 (m, 4H _{Arom})
	acidic 235 (30.6)	
7g	basic 235 (19.9); 307 (6.9)	2.04 (s, 3H, 6-CH ₃); 2.34 (s, 3H, <i>p</i> -CH ₃); 2.66 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 6.93-7.44 (m, 4H _{Arom})
	acidic 235 (28.6); 290 (8.0)	
7h	basic 239 (17.3); 305 (6.9)	2.04 (s, 3H, 6-CH ₃); 2.66 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 7.08-7.28 (m, 4H _{Arom})
	acidic 235 (27.8)	
7i	basic 243 (12.0); 307 (9.3)	2.04 (s, 3H, 6-CH ₃); 2.66 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 7.01-7.33 (4H _{Arom})
	acidic 235 (32.8)	
7l	basic 235 (28.6); 308 (12.1)	2.09 (s, 3H, 6-CH ₃); 2.69 (s, 6H, 4-N(CH ₃) ₂); 3.18 (s, 6H, 2-N(CH ₃) ₂); 3.80 (s, 3H, <i>p</i> -OCH ₃); 6.77-6.89 (2H _{Arom}); 6.98-7.10 (2H _{Arom})
	acidic 234 (32.0)	
7m	basic 239 (17.8); 273 (11.6); 300 (8.9)	2.05 (s, 3H, 6-CH ₃); 2.64 (s, 6H, 4-N(CH ₃) ₂); 3.15 (s, 6H, 2-N(CH ₃) ₂); 7.43-8.10 (4H _{Arom})
	acidic 236 (26.1); 260 (22.0)	
7n	basic 236 (26.3); 256 (21.6); 304 (13.6)	2.07 (s, 3H, 6-CH ₃); 2.67 (s, 6H, 4-N(CH ₃) ₂); 3.17 (s, 6H, 2-N(CH ₃) ₂); 7.24-7.41 (2H _{Arom}); 8.07-8.24 (2H _{Arom})
	acidic 233 (30.6); 269 (22.7)	
7o	basic 234 (7.8); 286 (6.3); 335 (0.7)	2.02 (s, 3H, 6-CH ₃); 4.47 (wide s, 2H, NH ₂); 4.67 (wide s, 2H, NH ₂); 7.13-7.45 (m, 5H _{Arom})
	acidic 230 (13.5); 273 (5.5); 338 (0.5)	

Table 3. Spectral data of isoquinolines (**8**).

Pro- duct	uv (methanol/water) ^{a)} medium	($\lambda_{\max}$ nm) ($\epsilon \cdot 10^{-3}$)	¹ H nmr (δ ppm, chloroform-d ₇ /TMS) ^{b)}
8e	basic	235 (10.7); 290 (5.4); 337 (5.0)	2.50 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.06 (s, 6H, N(CH ₃) ₂); 6.91 (q, J = 0.8 Hz, 1H, 4-H); 7.00-8.08 (m, 4H _{Arom})
	acidic	232 (10.0); 264 (9.5); 289 (7.3); 352 (8.1)	
8f	basic	240 (12.7); 297 (4.9); 334 (4.3)	2.45 (s, 3H, 6-CH ₃); 2.49 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.05 (s, 6H, N(CH ₃) ₂); 6.85 (q, J = 0.8 Hz, 1H, 4-H); 7.07-7.95 (m, 3H _{Arom} , 5, 7, 8-H)
	acidic	252 (19.3); 294 (5.8); 349 (7.3)	
8g	basic	233 (13.9); 290 (4.7); 342 (3.6)	2.47 (s, 3H, 7-CH ₃); 2.50 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.05 (s, 6H, N(CH ₃) ₂); 6.91 (q, J = 0.8 Hz, 1H, 4-H); 7.18-7.81 (m, 3H _{Arom} , 5, 6, 8-H)
	acidic	235 (17.9); 270 (10.7); 280 (11.0); 359 (7.8)	
8h	basic	245 (10.7); 310 (4.2); 337 (3.9)	2.50 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.06 (s, 6H, N(CH ₃) ₂); 6.85 (q, J = 0.8 Hz, 1H, 4-H); 7.13-8.00 (m, 3H _{Arom} , 5, 7, 8-H)
	acidic	219 (25.0); 255 (20.6); 298 (6.5); 354 (7.3)	
8i	basic	239 (12.1); 298 (4.9); 346 (3.5)	2.49 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.05 (s, 6H, N(CH ₃) ₂); 6.90 (q, J = 0.8 Hz, 1H, 4-H); 7.11-8.00 (m, 3H _{Arom} , 5, 6, 8-H)
	acidic	237 (17.0); 288 (10.0); 363 (6.8)	
8k	basic	224 (27.5); 246 (12.2); 326 (3.6)	2.48 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.04 (s, 6H, N(CH ₃) ₂); 3.87 (s, 3H, 6-OCH ₃); 6.77 (q, J = 0.8 Hz, 1H, 4-H); 6.80-8.05 (m, 3H _{Arom} , 5, 7, 8-H)
	acidic	222 (15.2); 264 (18.9); 343 (3.8)	
8l	basic	235 (20.5); 274 (6.2); 351 (4.7)	2.50 (d, J = 0.8 Hz, 3H, 3-CH ₃); 3.03 (s, 6H, N(CH ₃) ₂); 3.89 (s, 3H, 7-OCH ₃); 6.92 (q, J = 0.8 Hz, 1H, 4-H); 7.07-7.55 (m, 3H _{Arom} , 5, 6, 8-H)
	acidic	220 (25.7); 243 (25.0); 282 (10.8); 371 (7.5)	
8o	basic	225 (15.8); 292 (6.5); 335 (4.1)	2.47 (d, J = 0.8 Hz, 3H, 3-CH ₃); 5.15 (wide s, 2H, NH ₂); 6.83 (q, J = 0.8 Hz, 1H, 4-H); 7.23-7.75 (m, 4H _{Arom})
	acidic	237 (23.0); 274 (7.2); 284 (7.3); 338 (6.3)	

^{a)} Measured using a SPECORD M-40 spectrophotometer, basic medium: 0.02 m NaOH in 1 % methanol; acidic medium: 0.02 m HCl in 1 % methanol

^{b)} Obtained on a TESLA BS 587 NMR Spectrometer (80 MHz)

(M^+ , 100 %). Anal. Calcd for $C_{15}H_{19}N_4Cl$: C, 61.95; H, 6.59; N, 19.27; Cl, 12.19. Found: C, 62.10; H, 6.67; N, 19.09; Cl, 12.14. (7i) Ms (m/z): 290 (M^+ , 100 %). Anal. Calcd for $C_{15}H_{19}N_4Cl$: C, 61.95; H, 6.59; N, 19.27; Cl, 12.19. Found: C, 62.00; H, 6.71; N, 19.24; Cl, 12.05. (7l) Ms (m/z): 286 (M^+ , 100 %). Anal. Calcd for $C_{15}H_{22}N_4O$: C, 67.10; H, 7.74; N, 19.57. Found: C, 67.01; H, 7.83; N, 19.54. (7m) Ms (m/z): 301 (M^+ , 100 %). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.36; N, 23.24. Found: C, 59.90; H, 6.41; N, 23.06. (7n) Ms (m/z): 301 (M^+ , 100 %). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.36; N, 23.24. Found: C, 59.82; H, 6.47; N, 23.10. (8e) Ms (m/z): 186 (M^+ , 37.7 %). Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.30; H, 7.64; N, 15.06. (8f) Ms (m/z): 200 (M^+ , 29.5 %). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.90; H, 8.00; N, 14.10. (8g) Ms (m/z): 200 (M^+ , 36.8 %). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.99; H, 7.97; N, 14.04. (8h) Ms (m/z): 220 (M^+ , 28.4 %). Anal. Calcd for $C_{12}H_{13}N_2Cl$: C, 65.30; H, 5.94; N, 12.70; Cl, 16.06. Found: C, 65.25; H, 6.01; N, 12.75; Cl, 15.99. (8i) Ms (m/z): 220 (M^+ , 39.4 %). Anal. Calcd for $C_{12}H_{13}N_2Cl$: C, 65.30; H, 5.94; N, 12.70; Cl, 16.06. Found: C, 65.38; H, 5.82; N, 12.77; Cl, 16.03. (8k) Ms (m/z): 216 (M^+ , 37.5 %). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 72.31; H, 7.30; N, 13.00. (8l) Ms (m/z): 216 (M^+ , 58.8 %). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 72.27; H, 7.42; N, 12.92.

REFERENCES

1. W. Zieliński, *Polish J. Chem.*, 1982, **56**, 93
2. W. Zieliński, *Heterocycles*, 1985, **23**, 1639
3. L. I. Kriven and D. J. Cota, *Org. React.*, 1969, **17**, 213
4. W. Zieliński, *Synthesis*, 1980, 70
5. W. Zieliński and M. Mazik, *Polish J. Chem.*, 1993, **67**, 1099
6. W. Zieliński and M. Mazik, *Heterocycles*, 1993, **36**, 1521
7. B. I. Sukhorukov and A. I. Finkel'shtein, *Optika i Spektroskopiya*, 1960, **9**, 46
8. W. Zimmermann and K. Eger, *Arch. Pharm.*, 1979, **312**, 552
9. A. Miller, *J. Org. Chem.*, 1984, **49**, 4072
10. E. A. Arytyunyan, V. J. Gunar, and S. J. Zawalov, *Izv. Akad. Nauk SSSR*, 1970, 904
11. P. B. Russel and G. H. Hitchings, *J. Am. Chem. Soc.*, 1951, **73**, 3763
12. F. W. Bergstrom and R. E. Peterson, *J. Org. Chem.*, 1945, **10**, 479

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