A SIMPLE METHOD FOR SYNTHESIS OF 4-DIMETHYLAMINO-2,6-DIMETHYL-5-PHENYLPYRIMIDINES

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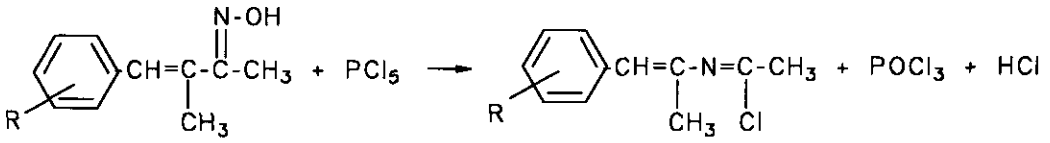
Abstract - The reaction of *N*-(1-methyl-2-phenylvinyl)acetimidoyl chloride and its derivatives substituted at the benzene ring with *N,N*-dimethylcyanamide was studied. At the first stage, linear products like 1-chloro-1-dimethylamino-3,5-dimethyl-6-phenyl-2,4-diaza-1,3,5-hexatrienes were obtained. They underwent cyclization to 4-dimethylamino-2,6-dimethyl-5-phenylpyrimidines in alkaline medium at elevated temperature.

A progress in developing the methods for synthesis of *N*-vinylimidoyl compounds observed in recent years[1-3] allowed to use them in synthesis of heterocyclic nitrogen compounds. Isoquinoline,[2,4] phenanthridine,[5] benzoxazole,[6-8] benzotriazole[9] and benzimidazole[10] derivatives were synthesized in cyclization of *N*-vinylimidoyl compounds. Reactions of *N*-vinylimidoyl compounds with acetylene dienophiles yield pyridine derivatives,[11] whereas with alkyl and aryl cyanides yield pyrimidine[2,3] and quinazoline[12] derivatives. Reactions of *N*-vinylimidoyl compounds with cyanamide and its *N,N*-disubstituted derivatives were not yet examined.

In this work, 4-dimethylamino-2,6-dimethyl-5-phenylpyrimidine and its derivatives substituted at the benzene ring were synthesized in reaction of *N*-(1-methyl-2-phenylvinyl)acetimidoyl chlorides with dimethylcyanamide.

N-(1-methyl-2-phenylvinyl)acetimidoyl chlorides (**2**) were obtained by Beckmann rearrangement of the oximes of 4-phenyl-3-methyl-3-buten-2-ones (**1**) in the presence of PCl_5,[1] and were used for further reaction after the removal of most $POCl_3$ and HCl.



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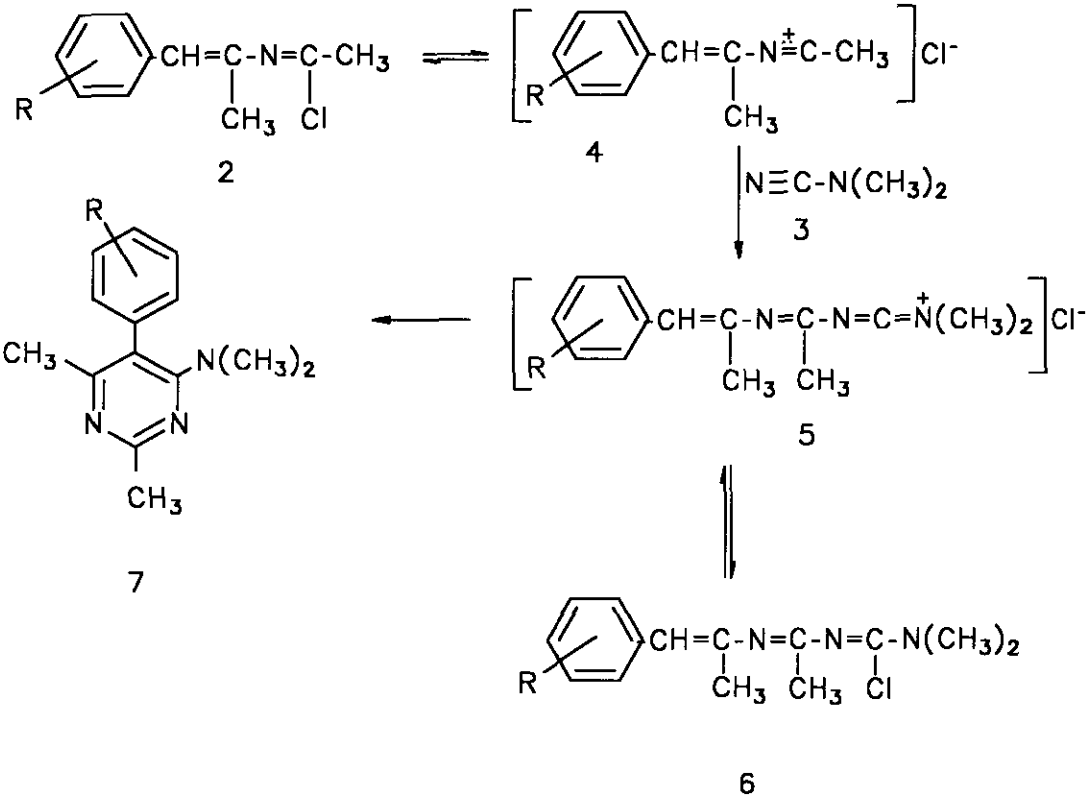
Considering the fact that *N*-vinylimidoyl compounds have a 2-azabutadiene moiety, one may expect that these compounds will react with dimethylcynamide following the typical thermal cycloaddition mechanisms.[13] However, we separated in the reaction of imidochlorides (**2**) with dimethylcyanamide the salt of linear compound (**6**) as a main reaction product, which suggests that the reaction follows a completely different course.

The determination of net atomic charges in starting imidochlorides[11] by a MNDO method indicates that the C-Cl bond is strongly polarized and may easily undergo a heterolytic cleavage with the formation of reactive *N*-(2-phenylvinyl)iminocarbenium cation (**4**). The assistance of the nitrogen atom having free electron pair facilitates this process.

The cation (**4**) can be susceptible to a nucleophilic attack of nitryl nitrogen atom in *N,N*-dimethyl-cyanamide (**3**) yielding the intermediate cation (**5**) that stabilizes itself forming the salt of compound (**6**) in acidic reaction medium due to the presence of strongly basic dimethylamino substituent.

Owing to the highly nucleophilic properties of nitryl nitrogen atom in **3**, the reaction proceeds quickly even at room temperature. Due to a high reactions rate, no by-products of cation (**4**) were observed, such as isoquinoline derivatives or fragmentation products which were obtained in large quantities in

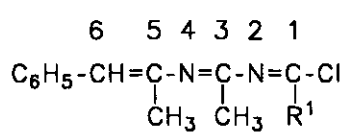


reaction of cation (**4**) with less reactive alkyl or aryl cyanides.[2]

Ring closure to a pyrimidine (**7**) proceeds through a cyclization of cation (**5**) at elevated temperature. As the MNDO computation showed (Table 1), the distribution of electron density in the salt of compound (**6**) is not favourable for a formation of cation (**5**) and the salt is stable in the reaction mixture.

The neutralization of the salt of compound (**6**) in low temperature leads to compound (**6**). In the compound (**6**) there is a strongly polarized C-Cl bond, that allows to obtain the pyrimidines (**7**) through the cation (**5**). The reaction of pyrimidine ring closure was carried out in boiling toluene which allowed to keep the appropiate reaction temperature.

Table 1. Net atomic charges of the selected atoms of compounds (**5a**), (**6a**) ($R^1 = N(CH_3)_2$) and salt of (**6a**) ($R^1 = NH(CH_3)_2$).



Compound	Cl	N in R^1	1-C	2-N	3-C	4-N	5-C	6-C
5a		-0.2883	0.3968	-0.1471	0.2209	-0.2233	-0.0482	0.0216
6a	-0.1706	-0.4455	0.3631	-0.2736	0.1707	-0.2619	-0.0009	-0.0610
salt of 6a	-0.0082	-0.0707	0.1625	-0.1843	0.1392	-0.2357	-0.0637	0.0816

Table 2. Pyrimidines (**7**) - yields and properties.

Product No.	R	Yield [a] % mol	bp (°C/Torr) or mp (°C)	Molecular formula	ms (70 eV) [b] m/z (rel. intens. %)
7a	-H	70	152-154/2.5	$C_{14}H_{17}N_3$	227 (M^+, 42.2)
7b	3-CH_3	68	160-162/2.5	$C_{15}H_{19}N_3$	241 (M^+, 39.7)
7c	3-OCH_3	55	158-160/1	$C_{15}H_{19}N_3O$	257 (M^+, 49.1)
7d	3-Cl	65	67.5-68.5	$C_{14}H_{16}N_3Cl$	261 (M^+, 38.6)
7e	3-NO_2	75	139-140	$C_{14}H_{16}N_4O_2$	272 (M^+, 30.4)
7f	4-CH_3	66	74-76	$C_{15}H_{19}N_3$	241 (M^+, 45.9)
7g	4-OCH_3	48	172-174/2.5	$C_{15}H_{19}N_3O$	257 (M^+, 40.9)
7h	4-Cl	60	135-136	$C_{14}H_{16}N_3Cl$	261 (M^+, 38.4)
7i	4-Br	55	118-120	$C_{14}H_{16}N_3Br$	305 (M^+, 36.1)
7k	4-NO_2	78	142-143	$C_{14}H_{16}N_4O_2$	272 (M^+, 39.2)

[a] Yield in relation to oxime

[b] Recorded on a Shimadzu QP-2000 spectrometer

Table 3. Spectral Data of Pyrimidines (**7**).

Pro-duct	uv (methanol/water)[a] medium (λ_{max} nm) (ε*10^{-3})	^{1}H nmr (δ ppm, acetone-d_6/TMS)[b]
7a	basic 263 (13.7) acidic 283 (13.9)	2.02 (s, 3H, 6-CH_3); 2.38 (s, 3H, 2-CH_3); 2.67 (s, 6H, $N(CH_3)_2$); 7.10 - 7.47 (m, $5H_{Arom}$)
7b	basic 265 (11.0) acidic 277 (13.5)	2.02 (s, 3H, 6-CH_3); 2.25 (s, 3H, m-CH_3); 2.35 (s, 3H, 2-CH_3); 2.69 (s, 6H, $N(CH_3)_2$); 7.01 - 7.26 (m, $4H_{Arom}$)
7c	basic 230 (23.4); 272 (9.7) acidic 236 (20.6); 247 (21.8); 282 (12.5)	2.03 (s, 3H, 6-CH_3); 2.38 (s, 3H, 2-CH_3); 2.70 (s, 6H, $N(CH_3)_2$); 3.78 (s, 3H, m-OCH_3), 6.70 - 7.20 (m, $4H_{Arom}$)
7d	basic 266 (10.8) acidic 277 (13.6)	2.04 (s, 3H, 6-CH_3); 2.39 (s, 3H, 2-CH_3); 2.70 (s, 6H, $N(CH_3)_2$); 7.17 - 7.42 (m, $4H_{Arom}$)
7e	basic 270 (16.9) acidic 272 (19.2)	2.06 (s, 3H, 6-CH_3); 2.41 (s, 3H, 2-CH_3); 2.70 (s, 6H, $N(CH_3)_2$); 7.66 - 8.26 (m, $4H_{Arom}$)
7f	basic 273 (12.7) acidic 281 (13.8)	2.02 (s, 3H, 6-CH_3); 2.35 (s, 3H, p-CH_3); 2.37 (s, 3H, 2-CH_3); 2.67 (s, 6H, $N(CH_3)_2$); 7.02 - 7.11 ($2H_{Arom}$); 7.16 - 7.25 ($2H_{Arom}$)
7g	basic 231 (12.9); 272 (10.6) acidic 228 (14.0); 280 (13.8)	2.02 (s, 3H, 6-CH_3); 2.37 (s, 3H, 2-CH_3); 2.68 (s, 6H, $N(CH_3)_2$); 3.80 (s, 3H, p-OCH_3); 6.87 - 6.98 ($2H_{Arom}$); 7.05 - 7.17 ($2H_{Arom}$)
7h	basic 224 (16.9); 268 (10.4) acidic 278 (14.9)	2.03 (s, 3H, 6-CH_3); 2.39 (s, 3H, 2-CH_3); 2.70 (s, 6H, $N(CH_3)_2$); 7.17 - 7.28 ($2H_{Arom}$); 7.38 - 7.48 ($2H_{Arom}$)
7i	basic 228 (17.0); 267 (10.1) acidic 275 (11.7)	2.04 (s, 3H, 6-CH_3); 2.38 (s, 3H, 2-CH_3); 2.69 (s, 6H, $N(CH_3)_2$); 7.13 - 7.39 ($2H_{Arom}$); 7.49 - 7.63 ($2H_{Arom}$)
7k	basic 266 (16.7); 335 (5.4) acidic 279 (19.2)	2.06 (s, 3H, 6-CH_3); 2.41 (s, 3H, 2-CH_3); 2.70 (s, 6H, $N(CH_3)_2$); 7.50 - 7.61 ($2H_{Arom}$); 8.21 - 8.32 ($2H_{Arom}$)

[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).

Structures of pyrimidine derivatives (**7**) were determined by microanalysis, ms, ^{1}H nmr and uv methods (Tables 2 and 3). The yields of pyrimidines (**7**) were high, ranging from 48 % to 78 % in relation to the starting oximes.

EXPERIMENTAL

N-(1-Methyl-2-phenylvinyl)acetimidoyl Chlorides (2 a - k)

A solution of 4-phenyl-3-methyl-3-buten-2-one oxime (**1 a - k**) (0.02 mol) obtained according to earlier described method,[14] in anhydrous benzene (100 ml) is added dropwise to a suspension of PCl_5 (4.8 g, 0.023 mol) in anhydrous benzene (50 ml) with simultaneous stirring and cooling. The reaction mixture is stirred and kept at room temperature, until the oxime decay is observed by tlc analysis (usually 5 to 15 min, 2 h in case of nitro derivatives). Imidoyl chlorides were used for further reaction after the removal of benzene with most of $POCl_3$ and HCl under vacuum at temperature not exceeding 20 °C.

1-Chloro-1-dimethylamino-3,5-dimethyl-6-phenyl-2,4-diaza-1,3,5-hexatriene (6a)

The imidochloride (**2a**) (3.86 g, 0.02 mol) is dissolved in anhydrous benzene (60 ml) and then *N,N*-dimethylcyanamide (1.4 g, 0.02 mol) is added. The solution is allowed to stand for 24 h. The benzene is separated, the obtained acidic oil is rinsed with anhydrous ether and finally neutralized with 5 % NaOH methanolic solution. Methanol is removed and the residual oil is extracted with chloroform to separate a salt. After the chloroform separation, a pure compound (**6a**) is obtained as yellowish oil in quantity of 4.9 g (93 %). ^{1}H Nmr ($CDCl_3$) δ 2.12 (d, 3H, CH_3, J = 1.3 Hz), 2.36 (s, 3H, CH_3), 2.80 (s, 6H, $N(CH_3)_2$), 6.96-7.48 (m, 6H, CH, C_6H_5); uv (methanol): λ_{max} ($\varepsilon \bullet 10^{-3}$) 265.5 (8.56). Anal. Calcd for $C_{14}H_{18}N_3Cl$: C, 63.75; H, 6.88; N, 15.93; Cl, 13.44. Found: C, 64.12; H, 6.74; N, 16.18; Cl, 12.92.

4-Dimethylamino-2,6-dimethyl-5-phenylpyrimidine and Derivatives (7 a - k)

Crude *N*-(1-methyl-2-phenylvinyl)acetimidoyl chloride (**2 a - k**), obtained from 0.02 mol of oxime (**1 a - k**), is dissolved in anhydrous benzene (60 ml) and *N*,*N*-dimethylcyanamide (2.8 g, 0.04 mol) is added. The solution is allowed to stand for 2 h at room temperature and then heated under reflux condenser for 30 min. To the reaction mixture, after cooling, NaOH solution in methanol (2.0 g, 0.05 mol in 30 ml of methanol) is added slowly. Solvents are removed under vacuum and anhydrous toluene is added to the residue. The mixture is kept boiling under reflux condenser until a decay of the intermediate product (**6**) is observed by tlc analysis (usually 3 h). After cooling, the mixture is acidified with 20 % HCl solution (30 ml) and purified by steam distillation. The acidic residue is filtered and the filtrate (about 50 ml) is alkalized with concentrated NaOH solution and extracted with ether. The crude product is purified by distillation or crystallization from n-hexane after a previous solvent removal.

Data of microanalysis of pyrimidines (**7 a - k**) were as follows: (**7a**) Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 73.87; H, 7.50; N, 18.63. (**7b**) Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.80; H, 7.87; N, 17.33. (**7c**) Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.09; H, 7.30; N, 16.49. (**7d**) Anal. Calcd for $C_{14}H_{16}N_3Cl$: C, 64.24; H, 6.16; N, 16.06. Found: C, 64.40; H, 6.25; N, 16.00. (**7e**) Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.90; H, 6.00; N, 20.45. (**7f**) Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.70; H, 8.01; N, 17.29. (**7g**) Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.20; H, 7.35; N, 16.23. (**7h**) Anal. Calcd for $C_{14}H_{16}N_3Cl$: C, 64.24; H, 6.16; N, 16.06. Found: C, 64.37; H, 6.20; N, 15.99. (**7i**) Anal. Calcd for $C_{14}H_{16}N_3Br$: C, 54.91; H, 5.27; N, 13.73. Found: C, 55.00; H, 5.21; N, 13.80. (**7k**) Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.80; H, 5.97; N, 20.40.

Microanalyses were performed with Perkin-Elmer 240 C analyzer. The physical and spectral data of the compounds are given in Table 2 and Table 3.

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