Syntheses with Nitriles. 60 (1). Preparation of 4-Amino-5-cyano-6-phenylpyrimidines from 2-Amino-1,1-dicyano-2-phenylethene

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Received April 22, 1980

The reaction of 2-amino-1,1-dicyanobut-1-ene and 2-amino-1,1-dicyano-2-phenylethene, respectively, with *N,N*-dimethylformamide dimethylacetal provided the corresponding (*N,N*-dimethylaminomethylene)amino derivatives. 2-[(*N,N*-Dimethylaminomethylene)amino]-1,1-dicyano-2-phenylethene was converted into 4-amino-5-cyano-6-phenylpyrimidines by treatment with primary aliphatic and aromatic amines. The structure of the reaction products was confirmed by ^{13}C nmr spectroscopy.

J. Heterocyclic Chem., **17**, 1385 (1980).

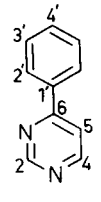
In a previous paper of this series (2) the reactivity of 2-amino-1,1-dicyanoethene with aldehydes and *N,N*-dimethylformamide dimethylacetal (DMFA), respectively, was studied. An unexpected cleavage of a C=C double bond was observed, and 1,1-dicyano-2-phenylethene and 1,1-dicyano-2-dimethylaminoethene, respectively, were formed. A comparable reaction was reported by Schmetzer, *et al.* (3), who considered the conversion of acrylic acid compounds into dimethylaminomethylene derivatives to be a multistep methylene exchange process. Subsequently, we examined the reaction of 2-amino-1,1-dicyanobut-1-ene (**1a**) (4) and 2-amino-1,1-dicyano-2-phenylethene (**1b**) (5), respectively, with DMFA. No cleavage of a C=C double bond takes place, but the expected dimethylaminomethylene derivatives **2a** and **2b** are isolated. These compounds should be starting materials for the preparation of substituted pyrimidines.

Little is reported about the use of dimethylaminomethylene derivatives of enaminonitriles for the use in synthesis of heterocycles. Albert and Ohta (6) treated 3-aminopyrazine-2-carboxamide with *N,N*-dimethylformamide and phosphoryl chloride to obtain 3-(dimethylaminomethyleneamino)pyrazine-2-carbonitrile, which was converted into substituted pteridines by reaction with amines. Foster and Elam (7) synthesized 4-aminoquinazolines, and received dimethylaminomethylene derivatives as intermediate products by reaction of isatoic anhydrides with ammonia, *N,N*-dimethylformamide and phosphorus oxychloride. Faganeli, *et al.* (8), reported the conversion of some amino heterocycles into dimethylaminomethylene derivatives and further reactions of those compounds.

Treating **2a** and **2b** with primary aliphatic and aromatic amines, we found that only **2b** was converted into the substituted pyrimidines **3a-m**. For the mechanism of that reaction can be assumed it starts with an amidine exchange by separating dimethylamine. The resulting

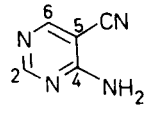
Table I

^{13}C-Chemical Shifts (ppm) (a)



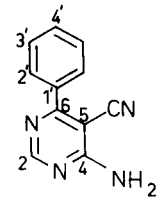
4

C-2, C-4	157.6
	157.8
C-5	112.8
C-6	161.2
C-1′	135.3
C-2′	126.1
C-3′	128.0
C-4′	130.2



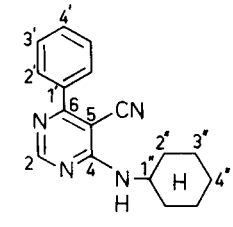
5

C-2	159.6
C-4	161.2
C-5	90.0
C-6	159.6
CN	114.8



3a

C-2	158.8
C-4	163.2
C-5	86.8
C-6	166.0
CN	116.0
C-1′	135.8
C-2′, C-3′	128.0
C-4′	130.5



3c

C-2	157.0
C-4	160.5
C-5	87.8
C-6	166.0
CN	115.5
C-1′	135.5
C-2′, C-3′	128.0
C-4′	130.7
C-1″	50.5
C-2″	32.9
C-3″, C-4″	25.5

(a) As solvent for **4**, **5** and **3a**, DMSO, for **3c**, chloroform was used.

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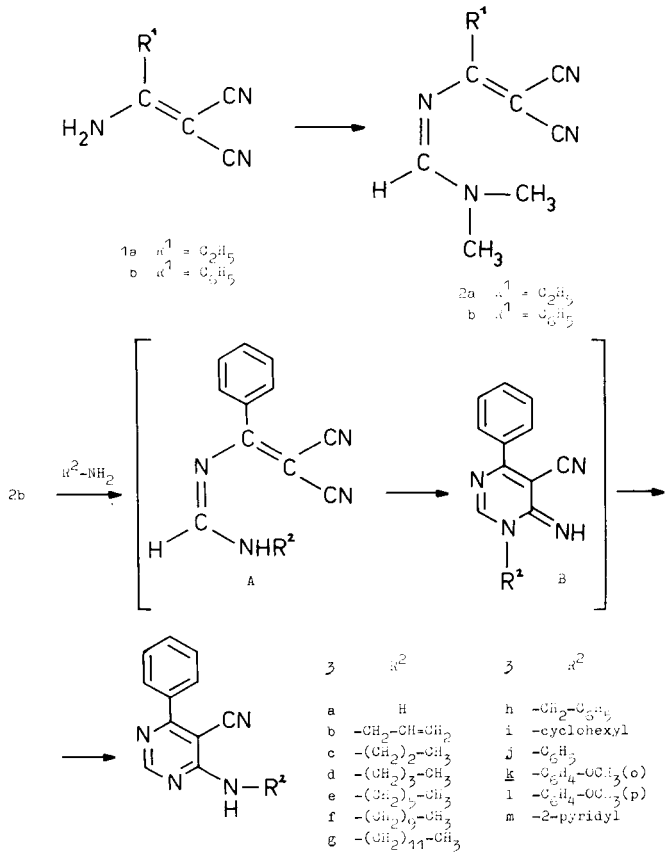

secondary amine of the aminomethylene compound A reacts with the nitrile group and leads to the cyclic imino derivative B. This intermediate product undergoes a Dimroth rearrangement, out of which the final product is **3**. Ir and pmr data, however, do not point to one of the three possible structures of the final product, which could either be the non cyclised aminomethylene derivative A, the cyclic imino derivative B or the rearranged product **3**. Only **3a** can be identified as 4-amino-5-cyano-6-phenylpyrimidine by comparing it with the product obtained by de Valk, *et al.* (9).

As other authors have reported (6,10,11), the reaction of *o*-aminonitriles with triethoxymethane leads to ethoxymethylene compounds, which are converted into aminomethylene derivatives or cyclic amines by careful treatment with amines. When heating those products in water or diluted alkali, immediate Dimroth rearrangement takes place. The high reaction temperature and the formation of dimethylamine facilitate the Dimroth rearrangement, and therefore the intermediates A and B cannot be isolated.

Structure **3** can definitely be confirmed by carbon-13 nmr data. Compounds **3a** (9), 4-phenylpyrimidine (**4**), and 4-amino-5-cyanopyrimidine (**5**) (12) have been investigated as references and data compared with those of compound **3c**. Especially compound **4** was useful in assigning the different signals. The carbon-13 shift of the C-atoms 2-6 of compound **3c** corresponds with the shift of the C-atoms of **3a** and **5**. The similar chemical shift of the C-atom 4 in **3a**, **5** and **3c** excludes the existence of the imino form B. Thus the compounds **3b-m** are identified as 4-alkyl- or arylamino-5-cyano-6-phenylpyrimidines (carbon-13 chemical shift data are given in Table I).

EXPERIMENTAL

All melting points were taken on a Büchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 421 Spectrometer (potassium bromide). Pmr spectra were measured on a Varian A-60 A instrument. A Varian HA-100 D spectrometer modified by Digilab Inc. was used for determining carbon-13 nmr spectra.

2-[(*N,N*-Dimethylaminomethylene)amino]-1,1-dicyanobut-1-ene (**2a**).

A suspension of 2-amino-1,1-dicyanobut-1-ene (1.0 g., 8.3 mmoles) (**1a**) (4) in *N,N*-dimethylformamide dimethylacetal (3.6 g., 30 mmoles) was refluxed for 1.5 hours. After cooling, some water was added, the precipitate was filtered by suction and recrystallized from aqueous methanol to produce colorless crystals, (1.0 g., 69%), m.p. 140°; ir: 2210 and 2190 (CN), 1640 and 1625 (C=C, C=N) cm^{-1}; pmr (deuteriochloroform): δ 1.18 (t, 3H, CH_3), 2.60 (q, 2H, CH_2), 3.07 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 7.80 (s, 1H, CH).

Table II

3	4-. . .-amino-5-cyano-6-phenylpyrimidine	Yield %	Recrystallisation Solvent	M.p., °C	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	—	97	methanol	192	$C_{11}H_8N_4$			28.55			28.11
b	-allyl-	58	aqueous methanol	93	$C_{14}H_{12}N_4$	71.17	5.12	23.71	71.18	5.10	23.64
c	-*n*-propyl-	59	aqueous methanol	114	$C_{14}H_{14}N_4$	70.57	5.92	23.51	70.53	5.78	23.50
d	-*n*-butyl-	48	aqueous acetic acid	103	$C_{15}H_{16}N_4$	71.40	6.39	22.20	71.49	6.31	22.24
e	-hexyl-	43	aqueous methanol	92	$C_{17}H_{20}N_4$	72.83	7.19	19.98	72.56	7.10	19.78
f	-decyl-	76	aqueous ethanol	76	$C_{21}H_{28}N_4$	74.96	8.39	16.65	74.84	8.11	16.64
g	-dodecyl-	93	ethanol	79	$C_{23}H_{32}N_4$	75.78	8.85	15.37	75.74	8.68	15.25
h	-benzyl-	70	aqueous acetic acid	137	$C_{18}H_{14}N_4$	75.50	4.93	19.57	75.26	4.94	19.32
i	-cyclohexyl-	86	acetic acid	164	$C_{17}H_{18}N_4$	73.35	6.52	20.13	73.34	6.44	20.07
j	-phenyl-	44	acetic acid	237	$C_{17}H_{12}N_4$	74.98	4.44	20.57	74.69	4.43	20.51
k	-*o*-methoxyphenyl-	86	ethanol	150	$C_{18}H_{14}N_4O$	71.51	4.67	18.53	71.40	4.68	18.55
l	-*p*-methoxyphenyl-	93	acetic acid	217	$C_{18}H_{14}N_4O$	71.51	4.67	18.53	71.40	4.74	18.46
m	2-pyridyl-	59	aqueous methanol	135	$C_{16}H_{11}N_5$	70.32	4.06	25.63	70.26	4.08	25.67

Table III

Spectral Data of Compounds **3b-m**

	Ir (Potassium Bromide) cm^{-1}			Pmr δ, ppm		
	NH	CN	Solvent	NH	Aromatic Protons	CH
b	3340	2210	carbon tetrachloride	5.99	7.30-7.98	8.47
c	3350	2210	carbon tetrachloride	5.95	7.28-8.00	8.46
d	3340	2210	deuteriochloroform	5.74	7.33-7.98	8.58
e	3340	2220	carbon tetrachloride	6.00	7.28-7.99	8.44
f	3340	2220	deuteriochloroform	5.77	7.30-7.95	8.57
g	3340	2220	deuteriochloroform	5.75	7.30-7.96	8.53
h	3350	2210	deuteriochloroform	6.00	7.31-7.97	8.58
i	3340	2220	deuteriochloroform	5.50	7.32-7.95	8.57
j	3320	2210	DMSO-d_6	9.63	7.18-8.00	8.65
k	3380	2210	deuteriochloroform		6.75-8.35	8.63
l	3320	2220	DMSO-d_6	9.47	7.30-7.95	8.52
m	3390	2205	deuteriochloroform		6.75-8.35	8.70

Anal. Calcd. for $C_9H_{12}N_4$ (176.2): C, 61.34; H, 6.86; N, 31.79. Found: C, 61.45; H, 6.89; N, 31.67.

2-[(*N,N*-Dimethylaminomethylene)amino]-1,1-dicyano-2-phenylethene (**2b**).

A suspension of 2-amino-1,1-dicyano-2-phenylethene (1.0 g., 5.9 mmoles) (**1b**) (5) in *N,N*-dimethylformamide dimethylacetal (2.4 g., 20.0 mmoles) was refluxed for 2 hours. After cooling, 20 ml. of water was added and the precipitate was filtered by suction. Recrystallization from acetic acid furnished 1.2 g. (91%) of **2b**, m.p. 176°; ir: 2220 and 2210 (CN), 1640 and 1630 (C=C, C=N) cm^{-1}; pmr (deuteriochloroform): δ 3.00 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 7.00-7.40 (m, 6H, phenyl, CH).

Anal. Calcd. for $C_{13}H_{12}N_4$ (224.3): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.38; H, 5.50; N, 24.70.

4-Amino-5-cyano-6-phenylpyrimidine (**3a**).

A suspension of 2.24 g. (10.0 mmoles) of **2b** in 80 ml. of concentrated aqueous ammonia was heated under reflux for 0.5 hours and then chilled in ice. The precipitate which resulted was collected and recrystallized from methanol to produce colorless crystals, (1.9 g., 97%), m.p. 194° (reported (9), m.p. 195°).

Anal. Calcd. for $C_{11}H_8N_4$ (196.2): N, 28.55. Found: N, 28.11.

General Procedure for the Preparation of **3b-m**.

A suspension of 2.5 mmoles of **2b** was heated with 10.0 mmoles of the corresponding amine to 110-120° for 2 hours. Solid amines were used in molar amounts using, if necessary, *N,N*-dimethylformamide as solvent. After cooling and treating with aqueous methanol the solid was filtered by suction.

Analytical and spectral data are given in Tables II and III.

Acknowledgment.

We thank Dr. H. Sterk for the measurement and interpretation of carbon-13 nmr spectra.

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