SYNTHESIS OF 2H-PYRAZOLO[3,4-b]PYRIDINES FROM 1,1,2,2-TETRACYANOCYCLOPROPANES

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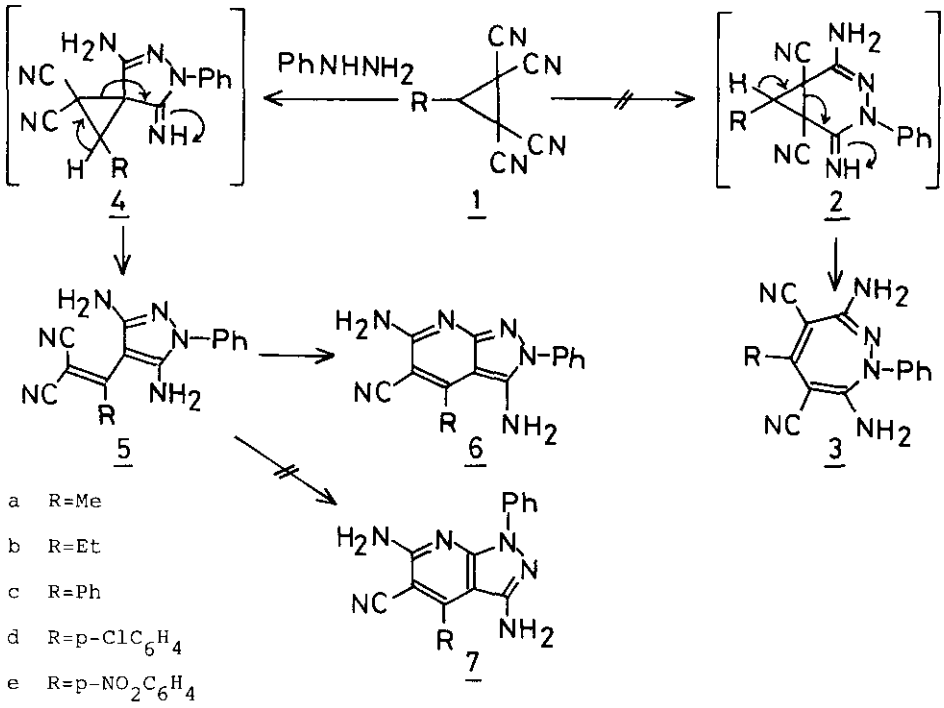
Abstract—— Reaction of 3-substituted 1,1,2,2-tetracyanocyclopropanes (1) with phenylhydrazine proceeded through the formation of pyrazole-4-spirocyclopropanes (4) followed by the ring opening of the cyclopropane ring to give 4-vinylpyrazoles (5), from which 2H-pyrazolo[3,4-b]pyridines (6) were obtained.

1,1,2,2-Tetracyanocyclopropanes (1) are expected to show characteristic chemical behaviors because of the presence of two sets of geminal electron-withdrawing cyano groups. The reactivities of 1, however, have attracted less attention in spite of their ready availability,[1] as compared with those of cyclopropanes activated by geminal two electron-withdrawing groups.[2] Hydrolysis of 3,3-dialkyl-1,1,2,2-tetracyanocyclopropanes followed by thermal ring opening of cyclopropanes was reported to give alkylidenesuccinimides.[3] Metallocyclobutane complexes were prepared from 1 on treatment with $Pt(Ph_3P)_4$ or $Pd(Ph_3P)_4$.[4] Recently, 2-azacycloheptatrienylidene was generated thermally from azacycloheptatriene-2-spiro-3'-tetracyanocyclopropanes.[5] In connection with the recent development in heterocyclic synthesis using cyclopropanes[6] and cyclopropenes[7] and with our interest in this field,[8] we examined the reactivities of 1 and have found a novel route to 2H-pyrazolo[3,4-b]pyridines (6).

3-Alkyl or aryl-1,1,2,2-tetracyanocyclopropanes (1a-e)[9] were treated with phenylhydrazine in MeOH at room temperature to give 1:1 addition products in



Scheme 1

43-57% yields (Table 1).

In the NMR spectra of the products, no absorptions of methine protons corresponding to the C_3-H of 1 were observed, and therefore cyclopropa[d]pyridazines (2) and pyrazole-4-spirocyclopropanes (4) were excluded as the initial 1:1 addition products (Scheme 1). Alternative possible structures for these products would be 1,2-diazepines (3), produced by the ring expansion of 2 or 4-vinylpyrazoles (5), formed by the ring opening of 4. However, 5 were finally chosen as the 1:1 addition products, since they were easily cyclized, as expected,[10, 11] to form 2H-pyrazolo[3,4-b]pyridines (6) in 46-81% yields (Table 2). The cyclization conditions depended upon the substituents as follows: a) a mixture of 5a or b and Et_3N in n-BuOH was refluxed, b) a mixture of 5c or d in 90% aq. MeOH containing 1% NaOH was stirred at room temperature, and c) a mixture of 5e in acetic anhydride was refluxed. Although another regioisomers, 1H-pyrazolo[3,4-b]pyridines (7), are possible for these cyclized products, it was difficult to distinguish between 6 and 7 on the basis of the spectral data and some attempted reactions. The structures were determined ultimately to be 6 by X-ray crystallography as

Table 1. Physical and Spectral Properties of Compounds 5

5	Yield (%)	Mp (°C)	MS (M^+)	IR (KBr, cm^{-1})	^1H-NMR[a] (δ, ppm)
a	50	266-268	264	3400, 3250, 3150, 2200, 1625, 1600	2.51 (s, 3H), 7.36-8.14 (m, 5H), 9.11 (broad)
b	48	247-249	278	3450, 3250, 3100 2200, 1620, 1560	1.20 (t, J=8 Hz, 3H), 2.89 (q, J=8 Hz, 2H), 7.34-8.16 (m, 5H), 9.21 (s)
c	57	211-213	326	3430, 3275, 3160, 2200, 1630, 1595	6.82-7.25 (m, 10H), 8.65 (broad)
d	43	215-217	360	3450, 3320, 3210, 2200, 1620, 1595	6.63-7.84 (m, 9H), 9.35 (s)
e	45	>300	-	3450, 3300, 3200, 2200, 1650, 1615	7.19-8.25 (m, 9H) 9.05 (broad)

[a]The solvents used were pyridine-d_5 for 5a and b, acetone-d_6 for 5c and d, and trifluoroacetic acid for 5e.

Table 2. Physical and Spectral Properties of Compounds 6

b	Yield (%)	Mp (°C)	MS (M^+)	IR (KBr, cm^{-1})
a	73	>300	-	3540, 3410, 3300, 3100, 2200, 1640
b	71	279-281	278	3540, 3260, 3080, 2200, 1640, 1580
c	72	290-292	326	3540, 3300, 3100, 2200, 1635, 1580
d	46	276-278	360	3600, 3420, 3255, 3140, 2200, 1635
e	81	>300	-	3450, 3340, 3220, 2200, 1625, 1605

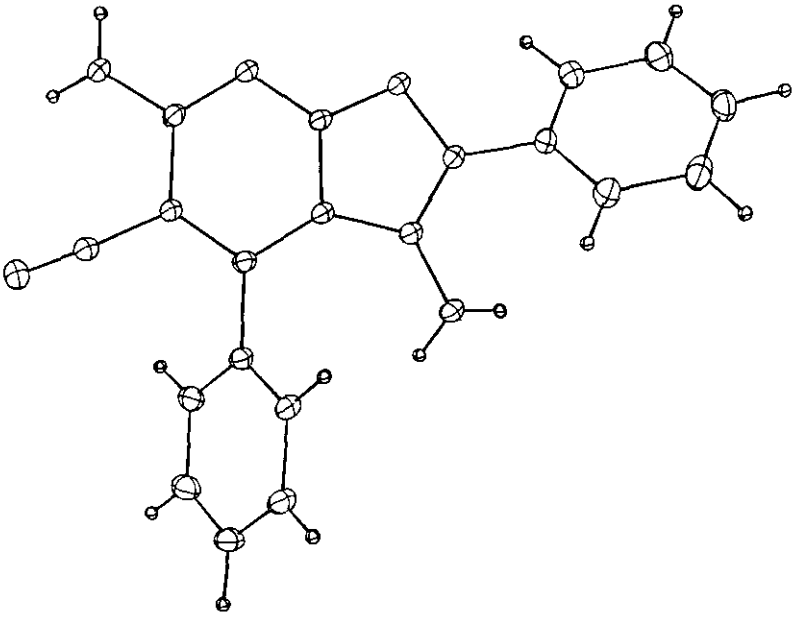


Fig. 1. Molecular structure of 6c.

shown in the Figure 1. This result is in accord with the observation[12] that acetylation of 3,5-diamino-4-phenylpyrazole occurred on the 3-amino group rather than the 5-amino one.

The present work revealed a new ring opening reaction of tetracyanocyclopropanes, which permits the ready access to multifunctionalized 2H-pyrazolo[3,4-b]pyridines.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. ^{1}H-NMR, IR, and mass spectra were measured with a JEOL JMX-60, a JASCO A-102, and a JEOL JMS DX-300 spectrometer, respectively. Microanalysis was performed with a Shimadzu UM-3B microanalyzer. X-ray diffraction data were obtained with a Phillips four-circle X-ray autodiffractomer by using Cu Kα (λ=1.54178 Å) radiation.

General Procedure for 3,5-Diamino-1-phenyl-4-(1'-substituted 2',2'-dicyanovinyl)-pyrazoles (5a-e).

To a stirred solution of 1 (4.0 mmol) in MeOH (12 ml), phenylhydrazine (6.0 mmol) was added. The reaction mixture was stirred at room temperature for 12-24 h. The resulting precipitates were collected by filtration and recrystallized from $CHCl_3$-DMF (5a, b) or MeOH-DMF (5c-e).

Table 3. Elemental Analysis for Compounds 5 and 6

Compounds	Formula	Calculated		Found	
		C	H	C	H
5a	$C_{14}H_{12}N_6$	63.62	4.58	63.49	3.91
5b	$C_{15}H_{14}N_6$	64.73	5.07	65.13	4.75
5c	$C_{19}H_{14}N_6$	69.92	4.32	70.08	4.31
5d	$C_{19}H_{13}N_6Cl$	63.25	3.63	63.25	3.72
5e	$C_{19}H_{13}N_7O_2$	61.45	3.52	61.72	3.75
6a	$C_{14}H_{12}N_6$	63.62	4.58	63.46	4.63
6b	$C_{15}H_{14}N_6$	64.73	5.07	64.76	5.03
6c	$C_{19}H_{14}N_6 \cdot CH_3OH$	67.03	5.06	66.81	5.07
6d	$C_{19}H_{13}N_6Cl$	63.25	3.63	63.03	3.88
6e	$C_{19}H_{13}N_7O_2$	61.45	3.53	61.33	3.73

Cyclization of 5a-e to 4-Substituted 3,6-Diamino-5-cyano-2-phenylpyrazolo[3,4-b]-pyridines (6a-e).

a) Compounds 6a and b: A mixture of 5a or b (0.5 mmol) and Et_3N (1 ml) in n-BuOH (20 ml) was refluxed for 8 h. After cooling, the precipitates were collected by filtration and recrystallized from MeOH (6a) or n-BuOH (6b).

b) Compounds 6c and d: A mixture of 5c or d (0.5 mmol) in 90% aq. MeOH (20 ml) containing 1% NaOH was stirred at room temperature for 2 h. The precipitates formed were collected by filtration and recrystallized from MeOH-DMF.

c) Compound 6e: A mixture of 5e (0.3 mmol) in acetic anhydride (10 ml) was refluxed for 2 h. After cooling, it was diluted with water (50 ml) and was allowed to stand overnight. The precipitates formed were collected by filtration and recrystallized from water-DMF.

Crystal Data for 6c.

$C_{19}H_{14}N_6 \cdot CH_3OH$ (recrystallized from DMF-MeOH), FW=358.40, triclinic, space group $P\bar{1}$, a=10.838, b=12.409, c=7.566 Å, α=110.37, β=84.52, γ=106.80°, V=913.18 $Å^3$, Z=2, D_c=1.304, D_m=1.297 g cm^{-3}, R=5.85%, 3257 independent reflections.

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