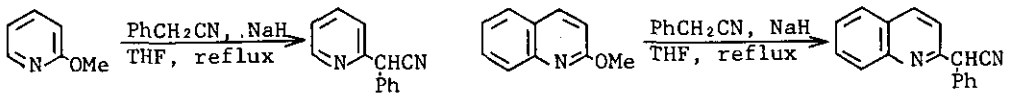
REACTIONS OF β-BROMO-N-HETEROAROMATICS WITH PHENYLACETONITRILE

Setsuya Ohba, Takao Sakamoto, and Hiroshi Yamanaka*
Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan

Abstract —— The reaction of 3-bromopyridine with phenylacetonitrile in the presence of NaH in THF gave a simple substitution product, α-phenyl-3-pyridineacetonitrile, whereas the reaction of 5-bromopyrimidine with phenylacetonitrile under similar conditions gave a ring-transformation product, 2-amino-5-bromo-3-phenylpyridine. 3-Bromoquinoline and 4-bromoisoquinoline underwent the former type reaction, while 3-bromo- and 3-chloroisoquinolines were converted into 2-amino-3-phenyl-1-naphthalenecarbonitrile according to the latter type reaction.

Previously, we reported that phenylacetonitrile, unlike other active methylene compounds, readily reacted with N-heteroaromatics containing a methoxyl group at their active positions (α- and γ-positions to the ring nitrogen atom), although a methoxyl group is recognized as a weak leaving group in nucleophilic substitution.[1] For example, the reaction of 2-methoxypyridine and 2-methoxyquinoline with phenylacetonitrile gave α-phenyl-2-pyridineacetonitrile and α-phenyl-2-quinolineacetonitrile, as shown below.

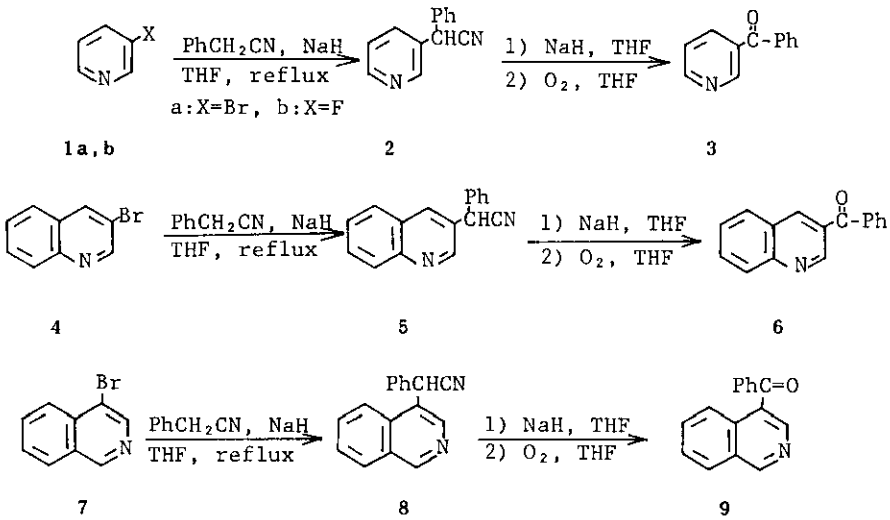


Scheme 1

These findings suggest the high potentiality of phenylacetonitrile for nucleophilic substitution. Thus, we investigated the reaction of phenylacetonitrile with β-halo-N-heteroaromatics which are, in principle, known to be inactive halides for nucleophilic addition-elimination process. Actually, it has been reported that 3-bromopyridine (1a) reacted with phenylacetonitrile in the presence of

sodium amide in toluene to give the substituted product (2), although the yield of 2 was poor.[2] In the present paper, we describe the formation of α-phenyl-N-heteroareneacetonitriles by the nucleophilic substitution of inactive N-heteroaryl halides, together with ring transformations from pyrimidine to pyridine and isoquinoline to naphthalene.

When 3-bromopyridine (1a) was heated with phenylacetonitrile in the presence of sodium hydride in THF under reflux, α-phenyl-3-pyridineacetonitrile (2) was obtained in 26% yield. 3-Fluoropyridine (1b), 3-bromoquinoline (4), and 4-bromoisoquinoline (7) smoothly underwent this reaction to give the corresponding α-phenyl-N-heteroareneacetonitriles (2, 5, and 8), respectively. These products were converted into the benzoyl derivatives (3, 6, and 9) by the reported method.[1]

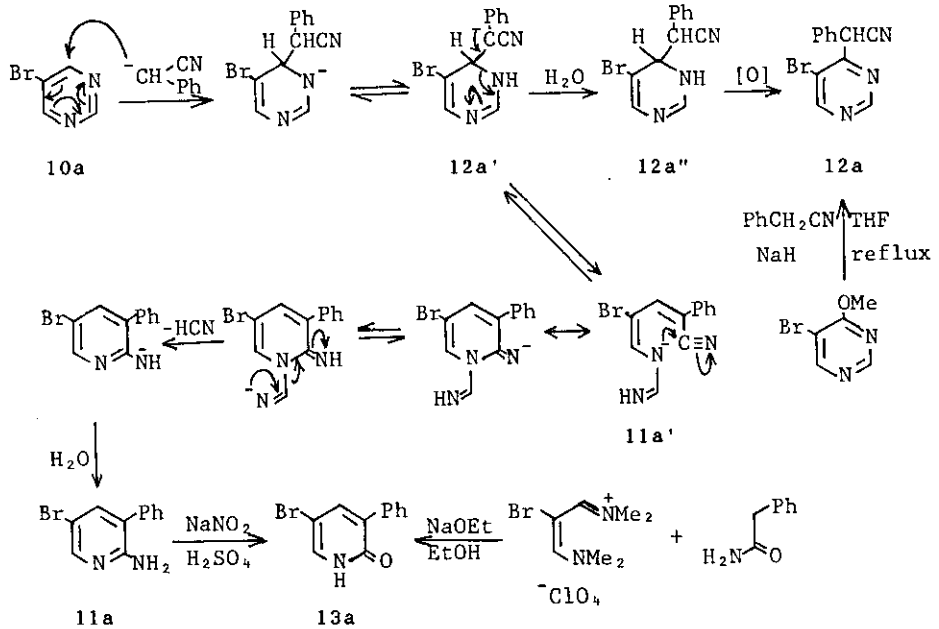


Scheme 2

In contrast to the above results, the reaction of 5-bromopyrimidine (10a) with phenylacetonitrile for 1 h gave 2-amino-5-bromo-3-phenylpyridine (11a) and 5-bromo-α-phenyl-4-pyrimidineacetonitrile (12a). The structures 11a and 12a were confirmed as follows. Compound 11a was converted into the corresponding pyridinone (13a) by diazotization with sodium nitrite in sulfuric acid, which was alternatively synthesized by the condensation of 1,3-bis(dimethylamino)-2-bromotrimethinium perchlorate and phenylacetamide. Compound 12a was synthesized by the substitution of 5-bromo-4-methoxypyrimidine with phenylacetonitrile carbanion.

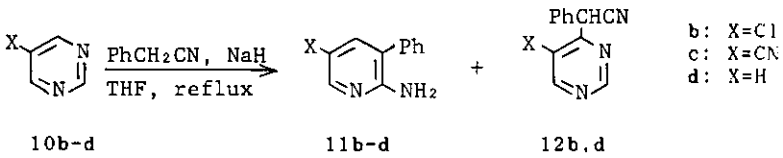
The mechanism of this unexpected reaction was considered as similar to that of the conversion of 5-nitropyrimidine with nitrile-stabilized carbanions into 2-amino-5-nitropyridine derivatives.[3] Namely, an initial addition of a carbanion to the

C_4-N_3 double bond of 10a forms an initial intermediate (12a'), then 12a' undergoes ring-cleavage reaction to give the second intermediate (11a') which recyclizes to 11a, accompanied by the loss of the iminomethine group for aromatization, according to the so-called S_{RN}ANRORC mechanism.[3] A concomitant formation of 12a suggests that the conversion may start from the addition of the carbanion to the C_4-N_3 double bond of 10a.



Scheme 3

When 10a was heated with phenylacetonitrile for 16 h, the yield of 11a increased, and 12a was not isolated from the reaction mixture, although 12a itself is stable under the conditions. This is evidence of the route from 10a to 11a via the intermediates 12a' and 11a', because the formation of 12a may be explained by autoxidation of 12a" derived from 12a' during usual work-up of the reaction mixture. In this mechanism, the substituent at the 5-position plays no role to progress of the reaction. In practice, the reaction of 5-chloropyrimidine (10b), 5-pyrimidinecarbonitrile (10c), and pyrimidine itself (10d) with the same reagent gave similar products (11b, 12b, 11c, 11d, and 12d). In the case of 5-methoxypyrimidine (10e), the starting material was recovered under similar conditions, probably due to the electron-donating character of the methoxyl group, which decreases the reactivity of the 4-position of the pyrimidine ring toward nucleophiles.

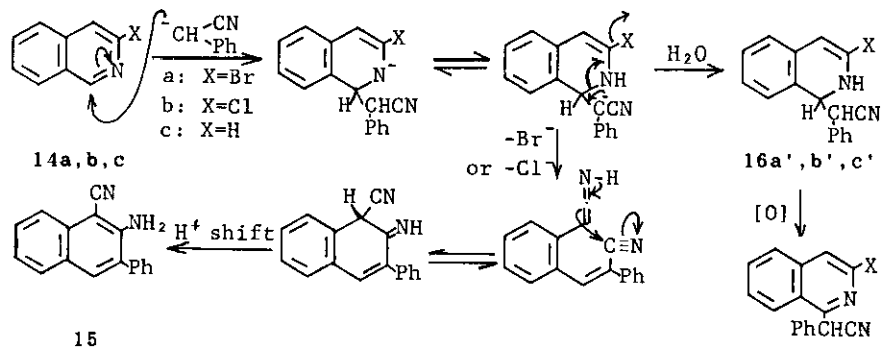


10b-d 11b-d 12b,d

Scheme 4

Similar ring-transformation was observed on the reaction of 3-bromoisoquinoline (**14a**) with phenylacetonitrile. In this case, when the reaction mixture was heated for 1 h under reflux, 3-bromo-α-phenyl-1-isoquinolineacetonitrile (**16a**) was obtained in 36% yield, together with 2-amino-3-phenyl-1-naphthalenecarbonitrile (**15**). Similarly to the reaction of **10**, prolonged reaction led to the selective formation of **15**. Thus, when **14a** was heated with phenylacetonitrile for 16 h, **15** was obtained as the sole product.

The mechanism of this reaction illustrated in Scheme 5 is in the same type to that in Scheme 3, although the difference in reactivity between 3-bromo- (**14a**) and 4-bromoisoquinoline (**7**) is not well explained by this consideration; the reaction of **7** with phenylacetonitrile did not give the adduct corresponding to **16a'**, but gave the substituted product (**8**).



14a,b,c 16a',b',c' 15 16a,b,c

Scheme 5

As the halogen atom at the 3-position acts as a leaving group in these cases, the behavior of 3-chloroisoquinoline (**14b**) was similar to that of **14a** giving **15** and **16b**, while the reaction of isoquinoline itself (**14c**) gave no naphthalene derivatives. In this case, most of isoquinoline was recovered with a small amount of α-phenyl-1-isoquinolineacetonitrile (**16c**). These findings may support our proposed mechanism.

EXPERIMENTAL

All melting points were determined by capillary method and are uncorrected. Proton magnetic resonance (^{1}H-nmr) spectra were recorded at 60 MHz on a JEOL JNM-PMX 60 spectrometer. Chemical shifts are quoted in δ value (ppm) with tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentanesulfonic acid sodium salt (DSS) as an internal standard, and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Infrared (ir) spectra were produced on a JASCO IR 810 spectrometer. Column chromatography was carried out on silica gel (NAKARAI CHEMICALS, Ltd. silica gel 60 or KATAYAMA CHEMICALS Ltd. silica gel 60).

General Procedure for the Reaction of β-Haloazines and the Related Compounds with Phenylacetonitrile ——— A 60% oil dispersion of NaH (0.18 g, 4.5 mmol) was washed with hexane, to which phenylacetonitrile (0.49 g, 4 mmol) in dry THF (20ml) was added, and the mixture was refluxed for 30 min. Then a β-haloazine (2 mmol) was added, and the mixture was refluxed under nitrogen atmosphere. After removal of the THF under reduced pressure, the residue was diluted with H_2O.

1) In the case of 1, 4, and 7: The aqueous solution was neutralized with 5% AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was subjected to silica gel column chromatography. Elution with hexane-AcOEt (9:1) gave the product (2, 5, or 8).

2) In the case of 10: The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was subjected to silica gel column chromatography. Elution with hexane-AcOEt (4:1) gave unreacted phenylacetonitrile, then elution with hexane-AcOEt (1:1) gave 11. The aqueous solution was neutralized with 5% AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was recrystallized from AcOEt to give 12.

3) In the case of 14: The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was subjected to silica gel column chromatography. Elution with hexane-AcOEt (9:1) gave 15. The aqueous solution was neutralized with 5% AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was recrystallized from hexane-AcOEt to give 16.

Table I. Reaction of β-Haloazines and the Related Compounds with Phenylacetonitrile

Substrate No.	Reaction Time (h)	Products No.	Yield (%)	No.	Yield (%)	Substrate No.	Reaction Time (h)	Products No.	Yield (%)	No.	Yield (%)
1a	20	2	26			10c	1	11c	68		
1b	5	2	73			10d	3	11d	20	12d	53
4	10	5	62			10d	10	11d	71		
7	10	8	58			14a	1	15	36	16a	36
10a	1	11a	28	12a	47	14a	16	15	71		
10a	16	11a	69			14b	1	15	48	16b	12
10b	1	11b	42	12b	18	14b	14	15	66		
10b	6	11b	63			14c	24	16d	7		

Table II. Melting Points and Spectral Data for the Products of the Reaction of β-Haloazines and the Related Compounds with Phenylacetonitrile

No.	mp (°C)	ir ($CHCl_3$) (cm^{-1})	^{1}H-nmr ($CDCl_3$) δ (ppm)
2	60-62[a]	2250	8.52(d,J=2,1H),8.49(dd,J=4,J=2,1H), 7.61(ddd,J=2,J=2,J=1,1H),7.5-7.1(m,6H),5.31(s,1H)
5	109-110	2240	8.83(d,J=4,1H),8.4-7.2(m,10H),5.35(s,1H)
8	101-102	2240	9.26(s,1H),8.62(s,1H),8.1-7.1(m,9H),5.72(s,1H)
11a	95-96	3500,3400	8.12(d,J=2,1H),7.7-7.3(m,6H),4.5(br,2H)
12a	65-66	2250	9.25(s,1H),8.83(s,1H),7.7-7.3(m,5H),5.67(s,1H)
11b	93-95	3500,3400	8.07(d,J=3,1H),7.7-7.3(m,6H),4.9-4.3(br,2H)
12b	65-66	2250	9.29(s,1H),8.74(s,1H),7.7-7.3(m,5H),5.69(s,1H)
11c	108-110	3520,3410,2250	8.38(d,J=2,1H),7.7-7.4(m,6H),5.6-4.9(br,2H)
11d	107-108	3510,3410	8.06(dd,J=5,J=2,1H),7.44(s,5H),7.33(dd,J=7,J=2,1H), 6.73(dd,J=7,J=5,1H),5.0-4.4(br,2H)
12d	117-118[b]	2150	9.25(d,J=1,1H),8.77(d,J=5,1H),7.7-7.3(m,6H), 5.24(s,1H)
15	121-123	3500,3400,2200	8.0-7.8(m,2H),7.8-7.2(m,8H),5.0-4.7(br,2H)
16a	148-150	2250	8.1-7.2(m,10H),5.98(s,1H)
16b	146-147	2250	8.3-7.3(m,10H),6.00(s,1H)
16c	139-141[c]	2250	8.53(d,J=5,1H),8.2-7.2(m,10H),5.86(s,1H)

a. Lit.[2] mp 63-65°C. b. Lit.[1] mp 117-118°C. c. Lit.[4] mp 143-145°C.

5-Bromo-3-phenylpyridin-2(1H)-one (13a) ——— 1) 1,3-Bis(dimethyamino)-2-bromotrimethinium perchlorate (0.37 g, 1 mmol) and phenylacetamide (0.14 g, 1 mmol) were added to a solution of EtONa in EtOH, prepared from metallic sodium (0.07 g, 3 mmol) and abs. EtOH (15 ml), and the mixture was refluxed for 5 h. After evaporation of the EtOH, the residue was diluted with H_2O and neutralized with dil. HCl. The resulting solid was collected by suction, dried in air, and recrystallized from EtOH to give colorless needles, mp 158-160°C. Yield 0.18 g (70%). ^{1}H-Nmr (DMSOd_6-DSS): 12.6-11.8 (br, 1H), 8.1-7.2 (m, 7H). Ir (KBr): 1645 cm^{-1}. 2) The compound 11a (0.25 g, 1 mmol) was dissolved in conc. H_2SO_4 (3 ml) and a solution of $NaNO_2$ (0.08 g, 1.2 mmol) in H_2O (1 ml) was added dropwise with stirring. After 20 min, H_2O (10 ml) was added, and the resulting solid was collected by suction, dried in air, and recrystallized from EtOH to give colorless needles, mp 158-160°C. Yield 0.22 g (89%).

5-Bromo-α-phenyl-4-pyrimidineacetonitrile (12a) ——— A 60% oil dispersion of NaH (0.18 g, 4.5 mmol) was washed with hexane, to which phenylacetonitrile (0.49 g, 4 mmol) in dry THF (20 ml) was added, and the mixture was refluxed for 30 min. Then 5-bromo-4-methoxypyrimidine (0.39 g, 2 mmol) was added, and the mixture was refluxed under a nitrogen atmosphere for 3 h. After removal of the THF under reduced pressure, the residue was diluted with H_2O. The aqueous solution was neutralized with 5% AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl, dried over $MgSO_4$, and evaporated. The residue was subjected to silica gel column chromatography. Elution with hexane-AcOEt (4:1) gave the product which was recrystallized from hexane-AcOEt to give colorless needles. mp 65-66°C, Yield 0.32 g (59%).

General Procedure for the Oxidative Decyanation of α-Phenyl-N-heteroareneacetonitriles into Benzoyl-N-heteroaromatics ——— A 60% oil dispersion of NaH (0.04 g, 1 mmol) was washed with hexane, to which α-phenyl-N-heteroareneacetonitrile (1 mmol) in dry THF (10 ml) was added, and the mixture was stirred for 5 min, while the evolution of hydrogen was ceased, and the mixture turned to reddish yellow. A current of oxygen was passed into the solution, until the solution turned to colorless. After evaporation of the solvent, H_2O (10 ml) was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated. The residue was recrystallized from an appropriate solvent or distilled *in vacuo* to give the product.

3-Benzoylpyridine (3) : A colorless liquid, bp 145°C/3 mmHg (lit.[5] bp 139-140°C/1 mmHg). Yield 0.17 g (94%). ^{1}H-Nmr ($CDCl_3$-TMS): 8.95 (d, *J*=2, 1H), 8.75

(dd, J=5, J=2, 1H), 8.10 (ddd, J=5, J=2, J=2, 1H), 8.0-7.7 (m, 2H), 7.7-7.2 (m, 4H). Ir ($CHCl_3$): 1665 cm^{-1}.

3-Benzoylquinoline (6) : Colorless needles from hexane, mp 76-78°C (lit.[6] mp 76-77°C). Yield 0.23 g (93%). ^{1}H-Nmr ($CDCl_3$-TMS): 9.20 (d, J=2, 1H), 8.5-8.4 (m, 1H), 8.3-7.3 (m, 9H). Ir ($CHCl_3$): 1660 cm^{-1}.

4-Benzoylisoquinoline (9) : Colorless needles from hexane, mp 79-80°C (lit.[7] mp 76-78°C). Yield 0.22 g (90%). ^{1}H-Nmr ($CDCl_3$-TMS): 9.40 (s, 1H), 8.65 (s, 1H), 8.3-7.3 (m, 9H). Ir ($CHCl_3$): 1660 cm^{-1}.

Table III. Analytic Data for the New Compounds

No.	Formula	Analysis (%) Calcd				Found			
		C	H	N	Cl or Br	C	H	N	Cl or Br
5	$C_{17}H_{12}N_2$	83.58	4.95	11.47		83.34	4.76	11.41	
8	$C_{17}H_{12}N_2$	83.58	4.95	11.47		83.50	4.83	11.38	
11a	$C_{11}H_9N_2Br$	53.04	3.64	11.25	32.08	52.95	3.46	11.05	31.99
12a	$C_{12}H_8N_3Br$	52.58	2.94	15.33	29.15	52.80	2.94	15.40	28.86
11b	$C_{11}H_9N_2Cl$	64.56	4.43	13.69	17.32	64.65	4.45	13.72	17.39
12b	$C_{12}H_8N_3Cl$	62.76	3.51	18.30	15.44	62.86	3.36	18.22	15.61
11c	$C_{12}H_9N_3$	73.83	4.65	21.52		74.05	4.61	21.53	
11d	$C_{11}H_{10}N_2$	77.62	5.92	16.46		77.58	6.08	16.35	
15	$C_{17}H_{12}N_2$	83.58	4.95	11.47		83.85	4.99	11.41	
16a	$C_{17}H_{11}N_2Br$	63.18	3.43	8.67	24.72	63.35	3.40	8.62	24.81
16b	$C_{17}H_{11}N_2Cl$	73.25	3.98	10.05	10.05	73.29	4.33	10.17	10.17
13a	$C_{11}H_8NOBr$	52.83	3.22	5.60	31.95	52.85	3.12	5.50	32.11

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Received, 5th April, 1990