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Benzyne Reaction. II.[1] Syntheses of Benzyl Cyanide Derivatives by Benzyne Reaction (Studies on the Syntheses of Heterocyclic Compounds. CCXLVII[2])

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Novel cyanomethylation of halogeno-benzene derivatives was investigated by benzyne reaction to give our expected variuos benzyl cyanides which seemed to be the important intermediates for amines (II) and acids (III).

One of the most important starting materials for the syntheses of isoquinoline derivatives is thought to be the benzyl cyanide derivatives (I), which have the alkoxy-substituents in the benzene ring, by the following reason. Cyclization of the amide (IV) which was obtained by condensation of the amine (II) with acid (III) derived from I would afford the expected isoquinoline derivative (V).

The purpose of the present investigation is to provide a novel synthetic method of I through benzyne reaction since it is a little troublesome, in general, to prepare the benzyl cyanide derivatives as the usual methods.

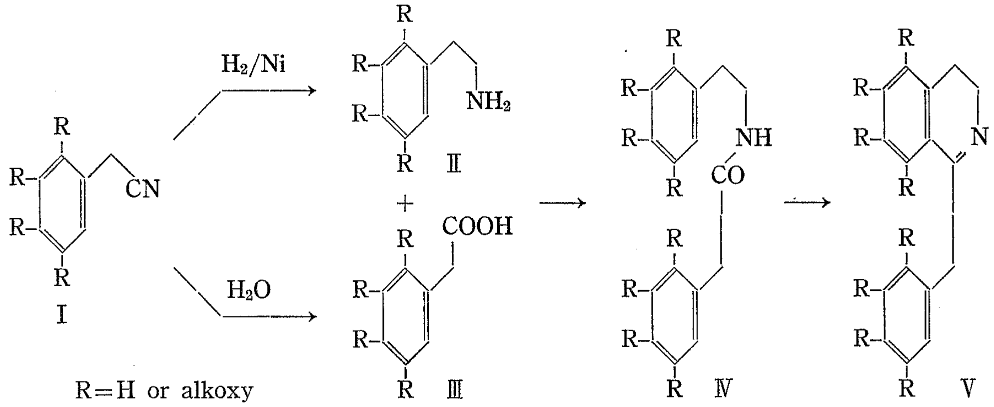

Chart 1

As an extension of the general benzyne-carbanion phenylation reaction,[4,5] the reaction of *o*-chlorobenzoic acid with certain nitrile in the presence of sodium amide and liquid ammonia has been reported by Biehle and Li,[6] but the example in case of the halogeno-compound having the alkoxy groups in the benzene ring has not yet been achieved in order to obtain our objective benzyl cyanide derivatives.

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[1] Part I: T. Kametani and K. Ogasawara, *J. Chem. Soc.* (C), **1967**, 2208.

[2] Part CCXLVI: *J. Chem. Soc.* (C), **1968**, 1619.

[3] Location: *No. 85, Kita-4-bancho, Sendai.*

[4] J.F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961); H. Heanly, *Chem. Rev.*, **62**, 81 (1962).

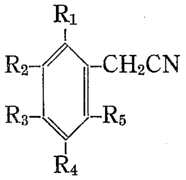
[5] *a*) F.W. Bergstrom and R.J. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945); *b*) P.H. Dirstini and F.W. Bergstrom, *J. Org. Chem.*, **11**, 55 (1946); *c*) R.A. Seibert and F.W. Bergstrom, *J. Org. Chem.*, **10**, 544 (1945); *d*) W.W. Leake and R. Levine, *Chem. Ind.* (London), **1955**, 1160; *J. Am. Chem. Soc.*, **81**, 1627, 1169 (1959).

[6] E.R. Biehl and Hsueh-Ming Li, *J. Org. Chem.*, **31**, 602 (1966).

To a mixture of sodium in liquid ammonia, which was prepared by using 4—6 molar equivalents of sodium for the halogeno-compound, was added 2—3 molar equivalents of acetonitrile. After the violent reaction during addition had been ceased, 1 molar equivalent of the chloro- and bromo-compound was added to the above reaction mixture, by the result of which our expected benzyl cyanide derivatives were obtained in a comparatively good yield. Althogh diphenylacetonitrile derivatives were formed as by-products in some case, it seems to be an excellent procedure for one-step synthesis of I, compared with the usual methods reported previously.

Table I shows the yields of the compounds (VI—XIII) which have been prepared by the reaction of 1 mole of halogeno-compound with about 3 moles of acetonitrile in the presence of about 5 moles of sodium amide.

Table I. The Yields of the Products in Case of Cyanomethylation of Halogenobenzene Derivatives by Benzyne Reaction



Starting materials	Compound	Product					Yield (%)	mp or bp (°C)
		R_1	R_2	R_3	R_4	R_5		
1-Chloro-2-methoxybezene	VI	H	OMe	H	H	H	68	bp 126—130 (4 mmHg)
2-Benzyloxy-1-chlorobenzene	VII	H	OCH_2Ph	H	H	H	42	bp 188—190 (3 mmHg)
1-Bromo-4-methoxybenzene	VIII	H	H	OMe	H	H	61	bp 114—116 (33 mmHg)
1-Chloro-4-methoxybenzene	VIII	H	H	OMe	H	H	61	bp 114—116 (33 mmHg)
3-Benzyloxy-4-methoxy-1-bromobenzene	IX	H	OCH_2Ph	OMe	H	H	52	mp 104—105
1-Bromo-2,3,4-trimethoxybenzene	X	H	OMe	OMe	OMe	H	36	mp 77.5—80
2-Bromo-1,4-dimethylbenzene	XI	Me	H	H	Me	H	66.5	bp 148—150 (22 mmHg)
1,2-Dichlorobenzene	XII	H	Cl	H	H	H	30.8	bp 112—120 (5 mmHg)
1,4-Dichlorbenzene	XIII	H	H	Cl	H	H	27.9	bp 117—121 (5 mmHg)

If the substitution reaction by cyanomethyl group would occur at its neighboring position of halogeno group, the above reaction would proceed through benzyne intermediates. As was shown in Table I, the cine substitution has occurred in case of 1-substituted-2-halogeno-compounds to give 3-methoxy-(VI, X) and 3-benzyloxybenzyl cyanide derivative (VII), whose syntheses were not so easy by the usual methods reported previously.7) On the other hand, the substitution of cyanomethyl group in case of 4-halogeno-compounds has occurred at the position attached by the halogeno-group.

Furthermore, cyanomethylation of 1,2-and 1,4-dichlorobenzene having two halogen atoms was also carried out, to give our expected compounds, (XII) and (XIII), respectively. Furthermore, hydrolysis of XII and XIII with an ethanolic alkaline solution afforded the corresponding acids (XVI and XVII), respectively.

In the above benzyne reaction, although the formation of bis(3-chlorophenyl)acetonitrile (XIV) could not be recognized, bis(4-chlorophenyl)acetonitrile (XV) was obtained as by-product, whose nuclear magnetic resonance (NMR) spectrum showed its characteristic pattern.

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7) E. Wong, *Tetrahedron Letters*, **1963**, 159.

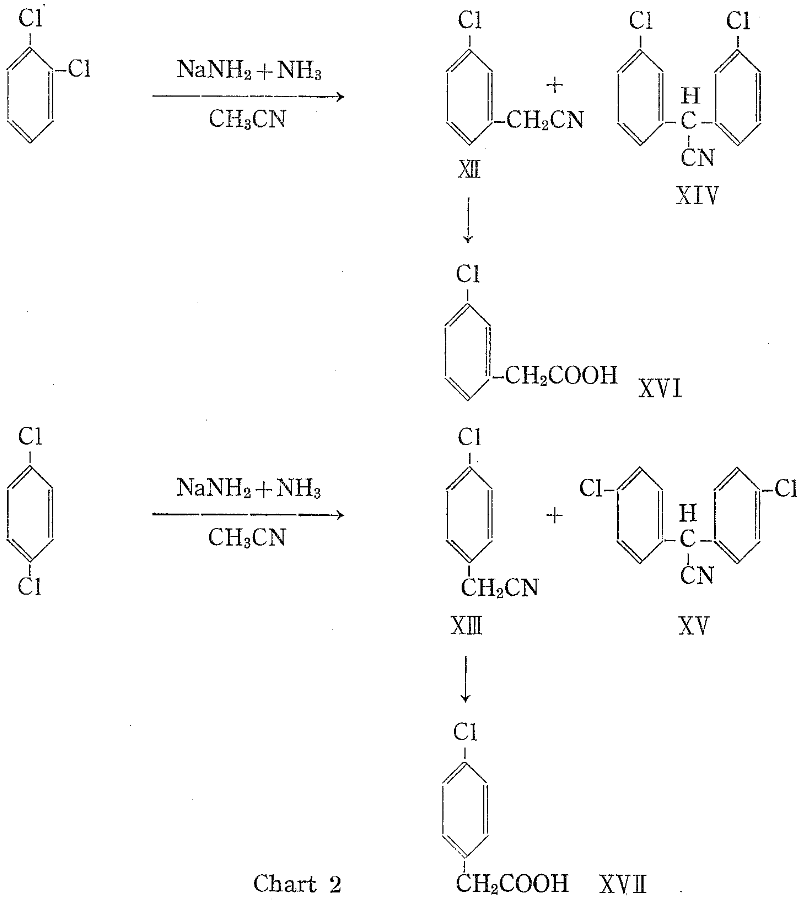

Chart 2

Experimental[8]

3-Methoxybenzyl Cyanide (VI)——To a stirred solution of 120 g (*ca.* 5 atom) of metallic Na in 2 liters of liq. NH_3 was added a small amount of $FeCl_3$, and the resultant mixture was stirred for 2 hr in order to prompt the formation of $NaNH_2$. To the above mixture was added carefully 120 g (*ca.* 3 mole) of acetonitrile within 5 min, and 130 g (0.915 mole) of 1-chloro-2-methoxybenzene was added rapidly to the above mixture. After the mixture had been stirred for further 4 hr, the excess of $NaNH_2$ was decomposed by addition of 200 g of NH_4Cl. The resultant mixture was poured into water and extracted with benzene. The extract was washed with 20% HCl aq. solution and then water, dried on K_2CO_3, and evaporated to give a brown oil, which was distilled *in vacuo* to afford 100 g (68%) of the nitrile (VI) as a colorless oil, bp 126—130° (4 mmHg) (lit.,[9] bp 124—128° (5 mmHg)). *Anal.* Calcd. for C_9H_9ON: C, 71.51; H, 6.61; N, 10.21. Found: C, 71.48; H, 6.85; N, 10.18.

Secondly, further distillation afforded 23 g (18.1%) of bis(3-methoxyphenyl)acetonitrile as a pale brown viscous syrup, bp 186—190° (4 mmHg), which was recrystallised from benzene to give colorless prisms, mp 88—89°. IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2180. NNR (τ) ($CDCl_3$): 6.36 (6H, singlet, $2OC\underline{H}_3$), 5.05 (1H, singlet, $\rangle C\underline{H}-CN$), 3.45—2.66 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.79; N, 5.53. Found: C, 75.85; H, 6.22; N, 5.36.

3-Benzyloxybenzyl Cyanide (VII)——To a solution of $NaNH_2$ [prepared from 1 liter of liq. NH_3, 32 g of Na, and a small amount of $FeCl_3$] in liq. NH_3 was added carefully 28.3 g of acetonitrile, and the mixture was stirred for 5 min. To the above mixture was added 50 g of 2-benzyloxy-1-chlorobenzene and the mixture was stirred for 3 hr. After the reaction, 74.5 g of NH_4Cl was added to the above reaction mixture to decompose an excess of $NaNH_2$.

The resultant mixture was admixed with an excess of water and extracted with benzene. The extract was washed with 20% HCl aq. solution (100 ml) and water, dried on K_2CO_3, and evaporated to give a brown oil, whose distillation *in vacuo* afforded 21.4 g (42%) of VII as a colorless oil, bp 188—190° (3 mmHg). *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.72; H, 6.05; N, 5.96.

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[8] All melting points were not corrected.

[9] H. Tsukamoto, H. Yoshimura, and S. Toki, *Chem. Pharm. Bull.* (Tokyo), 3, 239 (1955).

4-Methoxybenzyl Cyanide (VIII)——To a mixture of 100 g of Na (4.35 atom), 2 liters of liq. NH_3, and 123 g of acetonitrile (3 mole) was added with stirring 187 g (1 mole) of 1–bromo–4–methoxybenzene. The mixture was treated as usual to give 90 g (61%) of VIII as a colorless oil, bp 114—116° (3 mmHg) (lit.,[10] bp 152° (16 mmHg)).

Further distillation gave 21 g (16.6%) of bis(4–methoxyphenyl)acetonitrile, bp 210—220° (3 mmHg), which was solidified after cooling. Recrystallisation from EtOH afforded colorless needles, mp 154—155° (lit.,[11] mp 152—153°). IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2180. NMR (τ) ($CDCl_3$): 6.24 (6H, singlet, $2OC\underline{H}_3$), 5.06 (1H, singlet, $\rangle C\underline{H}$–CN), 3.15 (4H, doublet, $J=9$ cps, aromatic protons at C_3– and $C_{3'}$–positions), 2.80 (4H, doublet, $J=9$ cps, aromatic protons at C_2– and $C_{2'}$–positions). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.96; H, 6.21; N, 5.52.

3-Benzyloxy-4-methoxybenzyl Cyanide (IX)——To a solution of $NaNH_2$ in liq. NH_3 which was prepared from 1.5 liters of liq. NH_3 and 31 g of Na, was added carefully 33 g of acetonitrile and then 80 g of 3–benzyloxy–4–methoxy–1–bromobenzene.[12] The reaction mixture was treated with 73 g of NH_4Cl and worked up as usual. The benzene extract was washed with 20% HCl aq. solution (100 ml) three times and then water, dried on K_2CO_3, and evaporated to give a brown syrup, which solidified on being triturated with ether. Recrystallisation from benzene afforded 35 g (52%) of IX as colorless needles, mp 79—80° (lit.,[13] mp 80°). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.82; H, 6.00; N, 5.36.

3,4,5-Trimethoxybenzyl Cyanide (X)——To a stirred mixture of 8 g (*ca.* 0.35 atom) of Na, 100 ml of liq. NH_3 and 4 g (0.1 mole) of acetonitrile was added 10 g (*ca.* 0.04 mole) of 4–bromopyrogallol trimethyl ether.[14] The reaction mixture was treated as usual to give 3,4,5–trimethoxybenzyl cyanide as crystals, whose recrystallisation from EtOH afforded 3 g (36%) of pale yellow needles, mp 77.5—78° (lit,[15] mp 77°). IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2130.

2,5-Dimethylbenzyl Cyanide (XI)——To a stirred mixture of 70 g (*ca.* 3 atom) of Na, 1.5 liters of liq. NH_3 and 60 g (*ca.* 1.5 mole) of acetonitrile was added 50 g (*ca.* 0.5 mole) of 2–bromo–1,4–dimethylbenzene.[16] The reaction mixture was treated as usual to give 26 g (66.5%) of XI as colorless oil, bp 148—150° (22mmHg). IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2230. NMR (τ) (neat): 7.99 (3H, singlet, Ph–$C\underline{H}_3$), 7.88 (3H, singlet, Ph–$C\underline{H}_3$), 6.77 (2H, singlet, $PhC\underline{H}_2CN$), 3.14 (2H, singlet, aromatic protons), 3.05 (1H, singlet, aromatic proton). *Anal.* Calcd. for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.86; H, 7.80; N, 9.60.

3-Chlorophenylacetonitrile (XII)——A mixture of 1 liter of liq. NH_3, 144 g of Na and 0.4 g of $FeCl_3$ was stirred for 3 hr and then 132 g of acetonitrile was added to the above mixture, to which 152 g of 1,2–dichlorobenzene was added with stirring. When the excess NH_3 in the reaction mixture was evaporated to a volume of *ca.* 500 ml, the unreacted metallic Na and $NaNH_2$ were decomposed with 320 g of NH_4Cl and the resultant mixture was stirred for 40 min. After 100 ml of 60% dil. EtOH and then 700 ml of water had been added to the above mixture, which was stirred for 5 min and filtered. The filtrate was extracted with benzene. The extract was washed with 10% HCl aq. solution and water, dried on Na_2SO_4 and evaporated to give 83 g of a brown oil, which was distilled *in vacuo* to afford 46.6 g (30.8%) of a pale brown oil (XII), bp 112—120° (5 mmHg) (lit.,[17] bp 136° (10 mmHg)) and 5.6 g (2.13%) of an unknown compound as a reddish–brown oil, bp 179—185° (5 mmHg), whose structure could not be confirmed. Beilstein test of both specimens were positive. IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2220.

3-Chlorophenylacetic Acid (XVI)——A mixture of 46.6 g of the preceding nitrile (XII), 90 g of KOH, and 700 ml of EtOH was refluxed for 36 hr until the evolution of NH_3 gas has ceased. After removal of EtOH, a solution of the residue in water was extracted with benzene in order to remove an unreacted nitrile. The above aqueous layer was acidified with 10% HCl aq. solution and extracted with benzene. The extract was washed with water, dried on Na_2SO_4, and evaporated to give pale brown crystals, whose recrystallisation from *n*–hexane afforded 38.2 g (72.9%) of the acid (XVI) as pale yellow scales, mp 72—73° (lit.,[18] mp 74°). IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1710 (acid C=O).

4-Chlorophenylacetonitrile (XIII)——To a stirred mixture of 1 liter of liq. NH_3, 144 g of Na, 0.4 g of $FeCl_3$ was added 132 g of acetonitrile and then 152 g of 1,4–dichlorobenzene. The reaction mixture was treated by the same procedure as above to give 136.7 g of crude oil, whose distillation afforded 40.9 g (27.9%) of XIII as a colorless oil, bp 117—121° (5 mmHg) (lit.[18] bp 139° (12 mmHg)), and 13.4 g (5.1%) of XV as a yellow viscous oil, bp 185—190° (4 mmHg), both of which showed positive Beilstein test.

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[11] M. Rajsner, E. Adlerova, and M. Protiva, *Collection Czech. Chem. Commun.*, **28**, 1631 (1963).

[12] R. Robinson, E.M. Hindmarsh, and I. Knight, *J. Chem. Soc.*, **111**, 942 (1917).

[13] E. Wong, *Tetrahedron Letters*, **1963**, 159.

[14] R.P.G. Quelet, Fr. Patent 977613 [*C.A.*, **47**, 11247 (1953)].

[15] W. Baker and R. Robinson, *J. Chem. Soc.*, **1929**, 147.

[16] G.T. Morgan and E.A. Coulson, *J. Chem. Soc.*, **1929**, 2211.

[17] N. Campbell and J.E. Mckall, *J. Chem. Soc.*, **1948**, 1251.

[18] J.S. Buck and W.S. Ide, *J. Am. Chem. Soc.*, **54**, 3308 (1932).

XIII: IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2240. NMR (τ) (CCl_4): 6.37 (2H, singlet, $-C\underline{H}_2CN$), 2.75 (4H, singlet, aromtic protons).

XV: *Anal.* Calcd. for $C_{14}H_9Cl_2N$: C, 64.15; H, 3.46; N, 5.34. Found: C, 64.36; H, 3.73; N, 5.52. IR cm^{-1} ($CHCl_3$): $\nu_{C\equiv N}$ 2225. NMR (τ) ($CDCl_3$): 4.94 (1H, singlet, $>C\underline{H}-CN$), 2.74 (8H, singlet, aromatic protons).

4-Chlorophenylacetic Acid (XVII)——A mixture of 40.9 g of XIII, 160 g of KOH, and 1440 ml of EtOH was refluxed for 30 hr. After removal of the solvent the residue was treated as usual to give pale yellow crystals, whose recrystallisation from water afforded 45.1 g (98.1%) of the acid (XVII) as colorless needles, mp 101—102° (lit.,[19] mp 100°). IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1708 (acid C=O). *Anal.* Calcd. for $C_8H_7O_2Cl$: C, 56.32; H, 4.14. Found: C, 56.38; H, 4.59.

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