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Palladium-catalyzed Decomposition of Azides. I. Formation of Nitriles

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Palladium metal catalyzes the decomposition of benzyl azide affording benzonitrile, benzylamine, and *N*-benzylidenebenzylamine. The presence of a suitable hydrogen-acceptor improves the yield of benzonitrile at the sacrifice of benzylamine, whereas the yield of *N*-benzylidenebenzylamine remains constant. The reaction is applied to the preparation of other nitriles.

Azide group possesses many qualities that enable it an excellent starting group for organic synthesis. It can be introduced into an organic moiety by several convenient methods, even in the presence of various other functional groups.[1] The dipolar character and the reactivity (or instability) of the azide group make it react in a variety of fashions.[2] However, surprisingly little is known on its application to organic syntheses except for the syntheses of amines by reduction, carbonyl compounds by acid-catalyzed decomposition, and heterocyclic compounds by 1,3-dipolar addition. Some other transformations are restricted to azides of limited structures.[2]

In the course of our studies on the chemistry of the azide group,[3] we have found that a primary azide can be transformed into the corresponding nitrile by catalysis of palladium metal under such a mild condition as below 80 °C in neutral solutions. In this paper will be reported the procedure, scope, and limitation of the reaction.

It should be emphasized that the present procedure provides a method to obtain various nitriles *without* elongating the skeletal carbon-chain.

Results and Discussion

When a mixture of benzyl azide (**1**) and a catalytic amount of palladium black in benzene was refluxed for 30 min, benzonitrile (**2**), benzylamine (**3**), dibenzylamine (**4**), and *N*-benzilidenebenzylamine (**5**) were obtained in 43, 29, 2, and 27% yields, respectively.

$$\underset{\mathbf{1}}{PhCH_2N_3} \xrightarrow[PhH]{Pd^0} \underset{\mathbf{2}}{PhCN} + \underset{\mathbf{3}}{PhCH_2NH_2} + \underset{\mathbf{4}}{(PhCH_2)_2NH} + \underset{\mathbf{5}}{PhCH{=}NCH_2Ph}$$

The same, but a little bit slower, reaction took place at temperatures as low as 40 °C provided the mixture was set under an atmosphere of nitrogen. Ethanol could be replaced for benzene, whereas amines retarded the reaction appreciably. High-dilution technique, employed to avoid unnecessary bimolecular reaction of **1**, did not alter the yields of products. The results are summarized in Table 1.

Contrary, in the presence of a suitable compound such as 2,5-dimethyl-3-hexyne-2,5-diol or diphenylacetylene increased the yield of the nitrile greatly at the sacrifice of that of the amine (Table 2). Apparently these compounds play a role of a hydrogen-acceptor. Table 2 also shows that the high-dilution technique is effective when the reaction is run in the presence of a hydrogen-acceptor. Although in order to extend the scope of the reaction, one has to deal with azides of various types, some (especially low-molecular-weight aliphatic) azides are, unfortunately,

Table 1. Palladium-catalyzed decomposition of benzyl azide[a)]

Solvent	Temp. °C	Reaction Time, h	Conv. %[b)]	Yield of products, %[c)]			
				2	**3**	**4**	**5**
Benzene	40	1.5	100	43	26	—	26
Benzene	reflux	0.5	100	43	29	2	27
Benzene[d)]	reflux	0.25	100	45	29	3	22
Ethanol[e)]	reflux	0.5	100	45	19	—	27
Diethylamine	reflux	2.0	96	42	15	—	22
Butylamine	reflux	2.0	84	29	11	—	0.4

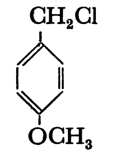
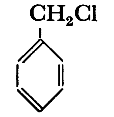
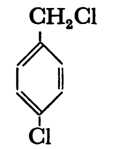
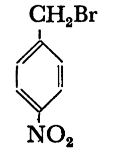
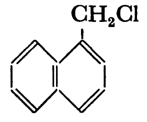
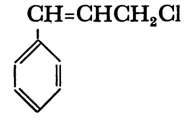
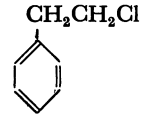
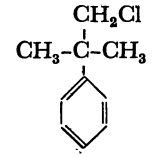
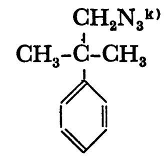
a) Method A. b) Consumed **1**. c) Based on **1** used. d) Method B. e) 99.5%.

Table 2. Effects of hydrogen-acceptors

Acceptor	Method	Conv. %[a)]	Yield of products, %[b)]			
			2	**3**	**5**	AH_2[c)]
$HOC(CH_3)_2C{\equiv}CC(CH_3)_2OH$ (**9**)	A	100	63	9	23	35(2)
$HOC(CH_3)_2C{\equiv}CC(CH_3)_2OH$	B	100	76	0	22	57(3)
$PhC{\equiv}CPh$ (**10**)	A	99	69	0	24	49(4)
$PhC{\equiv}CPh$	B	97	75	0	24	59(4)

a) Consumed **1**. b) Based on **1** used. c) Numbers out of and in parentheses are yields of *cis*- and *trans*-isomers, respectively. AH_2 denotes the reduced acceptor.

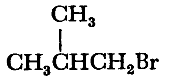
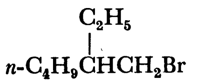
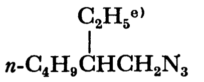
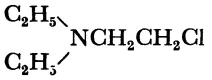
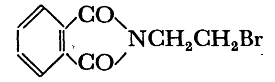
TABLE 3. PREPARATION OF ARYL AND ARALKYL NITRILES

	Azide-formation[a]		Nitrile-formation			
Halide	Temp °C	Time, h	Method	Acceptor[b]	Conv %[c]	Nitrile %[d]
	70	2	B	**9**	100	74
			B	**10**	100	73
	70	2	B	**9**	100	70
			B	**10**	100	68
	70	2	B	**9**	100	65
			B	**10**	100	65
	20	2	A[e]	**9**	99	57
			A[e]	**10**	82	52
	70	2.5	B	**9**	90	70
			A[f]	**10**	98	65
	40	2	B	**9**	99	56(2)[g]
			B	**10**	96	56(1)[g]
	70	15	B	**9**	100	72
			B	**10**	100	68
	140[h]	18	A[i,j]	—	100	47
			A[j]	**9**	21	7
			A[i,j]	**9**	15	3
			A[j]	—	18	3
	—	—	A[i,l]	—	99	47
			A[m]	**9**	87	77

a) Reaction in DMF. b) **9**; $HOC(CH_3)_2C{\equiv}CC(CH_3)_2OH$. **10**; $PhC{\equiv}CPh$. c) Azide consumed, assuming 100% conversion of the halide into the azide. d) Based on the halide used. e) Reacted for 2 h with the catalysis of palladium on charcoal. f) Reacted for 2 h. g) Numbers in parentheses are the yields of 3-phenylpropionitrile. h) Reaction in HMPA. i) Reaction with 100 mg of palladium on charcoal. j) Reacted for 12 h. k) A controlled experiment. l) Reacted for 2.5 h. m) Reacted for 16 h.

explosive and hazardous to be isolated.[4] Therefore, we have investigated a procedure to transform a halide into the corresponding nitrile without isolating the intermediate azide. Namely, benzyl chloride was reacted with sodium azide in dimethylformamide (DMF) at 70 °C for 2 h and the benzene-extract of the reaction mixture was subjected to the palladium-catalyzed decomposition. The results are listed in Table 3 together with those from substituted benzyl halides. Since the maximum yield of benzonitrile from benzyl azide was 75—76%, the present result is satisfactory. The distribution of the yield for *p*-methoxy-, *p*-chloro-, and unsubstituted benzonitrile may be accounted for by the different yields of the corresponding azides. The situation of *p*-nitrobenzonitrile is somewhat different: the reaction of *p*-nitrobenzyl bromide with sodium azide takes place more smoothly than those of other benzyl halides.

TABLE 4. PREPARATION OF ALIPHATIC NITRILES

Azide-formation[a]			Nitrile-formation				
Halide	Temp °C	Time, h	Method	Time, h	Acceptor[b]	Conv %[c]	Nitrile %[d]
$n\text{-}C_4H_9Br$	50	15	B	—	**9**	100	71
			B	—	**10**	100	70
$n\text{-}C_8H_{17}Cl$	70	15	B	—	**9**	100	81
			B	—	**10**	100	79
$n\text{-}C_{14}H_{29}Br$	70	15	B	—	**9**	100	76
			B	—	**10**	100	74
$n\text{-}C_{18}H_{37}Br$	50	15	B	—	**9**	100	88
			B	—	**10**	100	84
 $CH_3CH(CH_3)CH_2Br$	50	15	A	1.5	**9**	98	57
 $n\text{-}C_4H_9CH(C_2H_5)CH_2Br$	70	15	A	2	**9**	84	61
 $n\text{-}C_4H_9CH(C_2H_5)CH_2N_3$[e]	—	—	A	2	**9**	80	66
$HO(CH_2)_3Br$	75[f]	16	A	8	**9**	98	36
$AcO(CH_2)_3Br$	50	14	A	1	**9**	99	53
			A	5	**10**	78	54
 $(C_2H_5)_2NCH_2CH_2Cl$	70[f]	15	A	60	**9**	95	38
			A	60	**10**	69	37
	50	15	A	2	—	100	44
			A[g]	5	**9**	97	47

a) Reaction in DMF. b) See footnote (b) in Table 3. c) See footnote (c) in Table 3. d) See footnote (d) in Table 3. e) A controlled experiment. f) Reaction in water. g) Reaction with 100 mg of palladium on charcoal.

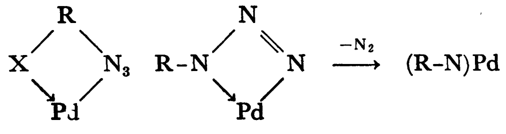
However, the p-nitro group behaves as a hydrogen-acceptor, which has been confirmed by a controlled experiment with benzyl azide and nitrobenzene, yielding a complex mixture of products. Palladium on charcoal was more effective catalyst than palladium black for this particular compound.

In Table 3 are also listed results on the reaction of phenethyl chloride and its analogs. It is interesting to note that the reaction of 3-azido-1-phenyl-1-propene proceeded without appreciable reduction of the internal double bond, whereas about 30% of styrene, *cis-* or *trans*-stilbene was reduced to the corresponding alkylbenzene when used as a hydrogen-acceptor for the decomposition of benzyl azide. This fact suggests that, unlike the nitro group, nonpolar carbon-carbon double bond has less facility to coordinate onto palladium than the polar azido group.

The decomposition of neophyl (2-methyl-2-phenylpropyl) azide is quite normal in the sense that it affords 2-phenyl-2-propyl cyanide in 47 and 77% yields in the absence and presence of a hydrogen-acceptor, respectively, whereas neophyl chloride gives the corresponding result only when it is subjected to the decomposition catalyzed by palladium on charcoal in the absence of a hydrogen-acceptor. Pre-treatment of the benzene extract by activated charcoal did not improve the yield when palladium black was used as a catalyst. The yield of neophyl azide from neophyl chloride was found to be 92%. Thus the factor(s) which affects the reaction starting from neophyl chloride is unpredictable.

The procedure has also been applied to aliphatic halides and the results are summarized in Table 4. Halides that have n-alkyl chain gave satisfactory results, whereas these branched at the β-position reacted less readily. Since neophyl azide reacts normally, the present result cannot be accounted for by steric effect, which is proposed for explaining the difference in reactivity of primary and secondary alkyl halides toward palladium.[5]

When a halide is substituted by a polar functional group, the reaction is greatly retarded and the yield of nitrile is reduced. The most extreme example can be seen in the reaction of *vic*-diazides: in spite of an expectation that the reaction of *vic*-diazides might afford α-amino nitriles, no decomposition of the azido group took place. This fact may be interpreted by the coordination of the functional group onto palladium (**6**) preventing the bidentate coordination of the azido group (**7**).[6] The latter coordination is necessary to loose the nitrogen-nitrogen bond to form an active species **8**.



6 **7** **8**

Experimental

Materials. Benzyl azide (bp 86—87 °C/20 mmHg (*lit*,7) 82.5 °C/16.5 mmHg), n_D^{14} 1.5407), *p*-chlorobenzyl azide (bp 80—82 °C/1.5 mmHg, n_D^{15} 1.5600),8) and diphenylacetylene (mp 60—61 °C (*lit*,9) mp 60—61 °C)) were prepared according to the literature, respectively. Halides, obtained from commercial sources or by well known methods, were purified by distillation or recrystallization prior to use. Solvents were distilled and kept over Molecular Sieves 4A. Other reagent-grade chemicals were used without further purification unless otherwise indicated.

2-Ethylhexyl Azide. A mixture of 2-ethylhexyl bromide (9.7 g, 0.05 mol) and sodium azide (6.5 g, 0.1 mol) in DMF (25 ml) was stirred at 70 °C for 15 h. The reaction mixture was poured into 250 ml of water and organic materials were extracted with one 100 ml portion of ether. The extract was washed with three 50 ml portions of water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residual oil was distilled yielding 5.8 g (74% yield) of 2-ethylhexyl azide: bp 81—82 °C/20 mmHg; n_D^{16} 1.4430; ν_{N_3} 2100 cm^{-1}. Found: C, 62.11; H, 11.10; N, 27.02%. Calcd for $C_8H_{17}N_3$: C, 61.89; H, 11.04; N, 27.07%.

Neophyl Azide. Starting from 8.4 g (0.05 mol) of neophyl chloride, 6.5 g (0.1 mol) of sodium azide, and 35 ml of hexamethylphosphoric triamide (HMPA), 6.1 g (70% yield) of neophyl azide was obtained: bp 90—91 °C/3 mmHg; n_D^{22} 1.5266; ν_{N_3} 2100 cm^{-1}. Found: C, 68.34; H, 7.73; N, 24.18%. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98%.

Procedure. *Method A.* A mixture of benzyl azide (2.0 mmol) and palladium black (10 mg) in benzene (4.0 ml) was refluxed for 30 min or stirred for 1.5 h at 40 °C under an atmosphere of nitrogen. It was necessary to exclude air from the system when the reaction was carried out without refluxing, otherwise no reaction took place even after 12 h.

To the reaction mixture were added 200 mg of biphenyl as an internal standard, 4 ml of ether, and 10 ml of water.

The ether extract was subjected to vpc analyses on Yanagimoto G1800 with a column of Silicon DC-200 (1 m, 150 °C, H_2 0.4 kg/cm^2) or BDS (1 m, 120 °C, H_2 0.2 kg/cm^2).

Method B. Into a refluxing mixture of palladium black (10 mg) and benzene (4.0 ml) was infused benzyl azide (2.0 mmol) over a period of 2 h. The whole mixture was refluxed for additional 15 min and the products were analysed as described above.

In some experiments 100 mg of palladium on charcoal (5%) was employed in place of palladium black yielding similar results. Ethanol could be substituted for benzene, but amines were not good solvents for the reaction (Table 1).

Method C. In a typical run, 20 mmol of a halide and 40 mmol of sodium azide in 10 ml of a solvent were stirred. The solvent, reaction temperature, and reaction period are shown in Tables 3 and 4. The reaction mixture was poured into water (100 ml) and 2.0 g of biphenyl (an internal standard for vpc analyses) was added. The organic materials were extracted with one 20 ml portion of benzene. The extract was washed with three 25 ml portions of water and dried over anhydrous sodium sulfate. A 2.0 ml aliquot of the benzene solution was subjected to palladium-catalysis with the Method A cr B and the products were analyzed on vpc as described above. When the reaction required more than an hour, only the Method A was employed.

Identification of Products. In a typical run 3.3 g (0.02 mol) of *p*-chlorobenzyl azide was added to a refluxing mixture of 2,5-dimethyl-3-hexyne-2,5-diol (2.8 g, 0.02 mol) and palladium black (0.1 g) in benzene (20 ml) over a period of 1 h and the whole mixture was refluxed for additional 10 min. The reaction mixture was filtered and the filtrate was washed with four 25 ml portions of water. The organic layer was dried over $CaCl_2$ and the solvent was evaporated *in vacuo* The residue was distilled at a bath temperature of 95 °C under a pressure of 20 mmHg.

The distillate was recrystallized from cyclohexane giving 1.6 g (60% yield) of *p*-chlorobenzonitrile: mp 91—93 °C (*lit*,10) mp 89—91 °C).

The nonvolatile substance was recrystallized from hexane giving 0.5 g (20% yield) of *N*-(*p*-chlorobenzyliden)-*p*-chlorobenzylamine: mp 58—60 °C (*lit*,11) mp 62—65 °C).

The aqueous layers were combined and extracted with 50 ml of ether. The ether layer was washed with three 25 ml portions of water and dried over $CaCl_2$. The solvent was evaporated *in vacuo* and the residue was recrystallized from benzene yielding 1.0 g (40% yield) of *cis*-2,5-dimethyl-3-hexene-2,5-diol: mp 68—69 °C (*lit*,12) mp 68—69 °C).

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