C-Alkylation of Active Methylene Compounds by Means of Alcohol. V.¹⁾ Benzylation of Aromatic Acetonitriles

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A simple method for the mono-benylation of aromatic acetonitriles is described. The method consists of heating the nitrile with benzyl alcohol in the presence of metallic sodium and benzyl acetate at 170–180°. The cyanide functions were protected from hydrolysis at the expense of benzyl acetate. The mechanism is discussed.

Among the aryl-aliphatic nitriles subject to alkylation, phenylacetonitrile is especially reactive and its methylene hydrogens are readily replaced by one or two alkyl groups. The benzylation of this substance is most commonly performed³⁾ with benzyl chloride in the presence of finely powdered sodium amide in an inert solvent.

The preliminary communication⁴⁾ from this laboratory reported several examples of benzylation of phenylacetonitrile and related nitriles (I) by means of benzyl alcohol and sodium. (Chart 1). The present paper is concerned with the detailed study of the reaction and additional comments about the mechanism.

Chart 1

Benylation of phenylacetonitrile by means of benzyl alcohol was first attempted by Sprinzak.⁵⁾ With potassium hydroxide as catalyst α,β -diphenylpropionic acid (IV), instead of α,β -diphenylpropionitrile (III), was obtained as a sole product in 45% yield.

Chart 2

The formation of IV as potassium salt indicated that the desired α,β -diphenylpropionitrile (III) which once formed as an intermediate underwent alkaline hydrolysis to afford the acid (IV) according to the sequence (II→III→IV). The formation of IV *via* phenylacetic acid (V)

1) Part IV: S. Miyano and N. Abe, *Chem. Pharm. Bull.* (Tokyo), **15**, 1810 (1967).

2) Location: Nanakuma, Fukuoka.

3) F.W. Bergstrom and W.C. Fernelius, *Chem. Rev.*, **12**, 135 (1933); **20**, 451 (1939).

4) S. Miyano and N. Abe, *Tetrahedron Letters*, **1966**, 1509.

5) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).

is not tenable in view of our failure to isolate IV when phenylacetic acid (V) was subjected to this type of benzylation.

Under the highly basic conditions employed and the presence of water formed hydrolyses of nitriles, III to IV, and II to V, were inevitable. The latter hydrolysis may account for the low yield of the product (IV).

From these observations it is essential to avoid the hydrolyses of nitriles in order to attain the successful benzylation of phenylacetonitrile. Accordingly the attention has been focused on protection of nitriles from hydrolysis. In the present study potassium hydroxide was replaced by metallic sodium to minimize the liberation of water. Key variation was addition of equimolar amount of benzyl acetate, choice of which was based on the following considerations: 1) The ester is much more susceptible to alkaline hydrolysis than nitrile. 2) Either of hydrolysates, *e.g.*, benzyl alcohol or sodium acetate is not harmful to the reaction system.

Thus, in the presence of sodium and benzyl acetate, the benzylation of a series of aromatic acetonitriles proceeded smoothly to give monobenzylation product in good yield (Table I).

TABLE I. α -Benzylated Nitriles

$\begin{array}{c} \text{R}-\text{CH}-\text{CN} \\ \\ \text{C}_6\text{H}_5-\text{CH}_2 \end{array}$										
R	mp (°C)	bp (°C) (mmHg)	Yield ^{a)} (%)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
Phenyl	57—58	150—155 (4)	85.2	C ₁₆ H ₁₃ N	86.92	6.32	6.76	87.07	6.43	6.58
<i>o</i> -Chlorophenyl	63—64.5 ^{b,c)}		39.0	C ₁₅ H ₁₂ NCl	74.53	5.01	5.80	74.33	5.03	5.62
<i>p</i> -Chlorophenyl	85—85.5 ^{b,d)}		82.6	C ₁₅ H ₁₂ NCl	74.53	5.01	5.80	74.65	4.95	5.60
1-Naphthyl	76—77 ^{e)}	215—225 (7)	64.0	C ₁₉ H ₁₅ N	88.68	5.88	5.44	89.06	5.79	5.41
2-Naphthyl	96—97 ^{f)}		75.5	C ₁₉ H ₁₅ N	88.68	5.88	5.44	89.05	5.83	5.64
2-Pyridyl	66—67 ^{b,g)}	170—175 (7)	84.0	C ₁₄ H ₁₂ N ₂	80.74	5.81	13.45	80.88	6.09	13.34
2-Quinolyl	66—67 ^{b,h)}		54.3	C ₁₈ H ₁₄ N ₂	83.68	5.46	10.85	83.42	5.25	10.76

a) Yields are based on nitriles.

b) new compounds

c) colorless prisms (from EtOH-H₂O)

d) colorless needles (from EtOH)

e) Melting point was reported as 75°: Buu-Hoi, P-Cagniant, *Rec. Trav.Chim.*, **64**, 355 (1943).

f) No melting point was mentioned in literature: *UCLAF Fr.*, 992, 104; *C.A.*, **50**, 15591 (1956).

g) colorless prisms (from EtOH-H₂O)

h) light-yellow platelets (from MeOH-H₂O)

All products were identified by elementary analyses, and infrared spectra and α,β -diphenylpropionitrile was further characterized by hydrolysis which gave the corresponding amide.

The low yield encountered with *o*-chlorophenylacetonitrile is presumably due to the steric hindrance involved.

In contrast, in the absence of benzyl acetate, the yields of α,β -diphenylpropionitrile (III) were much lower (average of two runs: 33%) and this obviously indicates that the use of equimolar amount of benzyl acetate is essential and the nitriles can be protected from hydrolysis at the expense of benzyl acetate.

While benzyl acetate and sodium were employed in slight excess, a large excess of benzyl alcohol, usually 3—4 times the calculated amount, was used since the alcohol could also serve as solvent. With less amount of alcohol precipitation of solid substance and subsequent decrease of the yield resulted.

The temperature is critical; the reaction temperature was maintained at 170—180° throughout and the yields in Table I were recorded at this temperature range. It was observed that the yields were dependent on reaction temperatures and at lower temperatures the yields showed a marked decrease for α,β -diphenylpropionitrile (Table II).

TABLE II. Effect of Varying the Temperature on Yield of α,β -Diphenylpropionitrile

Reaction temperature (°C)	Yield		Reaction temperature (°C)	Yield	
	(g)	(%)		(g)	(%)
145	4.8	46.4	165	7.2	69.6
155	5.0	48.3	170—180	8.8	85.2

This facile benzylation is considered to be the result of two consecutive reactions:

Chart 3

The first step involves condensation between nitrile and benzaldehyde to form intermediary benzylidene compound (VI). Addition of benzaldehyde is not necessary since it is gradually formed from benzyl alcohol by oxidation or dehydrogenation^{6,7} under the alkaline conditions used. In the second, the benzylidene compound is reduced by means of sodium and benzyl alcohol to the desired benzylated nitrile, the benzaldehyde reformed being used to the first step. The reducibility of α -phenylcinnamionitrile (VI, $\text{R}=\text{C}_6\text{H}_5$) by means of sodium and benzyl alcohol which ordinarily is incapable of reducing the isolated carbon-carbon double bond is apparently associated with the polar character involved in VI.

The mechanism just proposed has been confirmed by the preparation of α -phenylcinnamionitrile (VI, $\text{R}=\text{C}_6\text{H}_5$) by the condensation of phenylacetonitrile and benzaldehyde followed by the reduction of VI to α,β -diphenylpropionitrile (VII, $\text{R}=\text{C}_6\text{H}_5$) under the same conditions with the general procedure. The combined steps thus constitute a satisfactory rationalization of the course of this benzylation.

The present method for the benzylation of aromatic acetonitrile offers the advantage of experimental simplicity, good yield, and ready availability of alcohols over the conventional one using alkyl halides.

Experimental

Material—Commercially available phenylacetonitrile was purified by distillation. The following six aromatic acetonitriles were prepared according to the literature methods: *o*-chlorophenylacetonitrile,⁸⁾ *p*-chlorophenylacetonitrile,⁹⁾ 1-naphthylacetonitrile,⁹⁾ 2-naphthylacetonitrile,¹⁰⁾ 2-pyridylacetonitrile,¹¹⁾ 2-quinolylacetonitrile.¹²⁾

General Procedure—To a solution of sodium benzyolate in benzyl alcohol prepared from 0.06 mole of Na and 20 ml of benzyl alcohol was added dropwise at 170° a mixture of 0.05 mole of aromatic acetonitrile and 0.06 mole of benzyl acetate. The resulting mixture was stirred and refluxed for 2 hr at 170—180° and poured into H_2O . The resulting solution was extracted with ether, dried over K_2CO_3 and ether

6) M. Guerbet, *Bull. Soc. Chim. France*, [4] 3, 500 (1908).

7) W. Hüchel and H. Naab, *Chem. Ber.*, 64, 2137 (1931).

8) R. von Walther and L. Hirschberg, *J. Prakt. Chem.*, [2] 67, 377 (1903).

9) L.H. Briggs and J.M. Wilson, *J. Chem. Soc.*, 1941, 500.

10) M.S. Newmann, *J. Org. Chem.*, 9, 518 (1944).

11) K. Winterfeld and K. Flick, *Arch. Pharm.*, 26, 448 (1956).

12) V. Carelli, M. Cordellini, and F. Liberatore, *Ann. Chim. (Rome)*, 49, 709 (1959).

removed. The residue was purified by recrystallization or distillation under reduced pressure to give benzylate product. IR spectra of all the product in Table I have absorptions at 2225—2245 cm^{-1} ($\text{C}\equiv\text{N}$).

Attempted Benzylation of Phenylacetic Acid—An attempt to benzylate phenylacetic acid with benzyl alcohol and Na failed, all starting material recovered as Na-salt.

α,β -Diphenylpropionamide—A suspension of 10 g of α,β -diphenylpropionitrile in 100 g of 80% sulfuric acid was heated with good stirring for 30 min during which the temperature of the reaction was maintained at 88—93°. The mixture was poured onto ice, the resulting precipitate collected, and washed with 10% aqueous K_2CO_3 . Recrystallization from EtOH- H_2O gave colorless needles, mp 131—132°. ¹³⁾ Yield 7.8 g (71.8%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3435, 3220, 1656 ($-\text{CONH}_2$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{ON}$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.83; N, 6.08.

Experiments Supporting the Proposed Mechanism

α -Phenylcinnamonitrile—An intermediate of the reaction was prepared by the condensation of phenylacetonitrile with benzaldehyde under the conditions assimilated with that of the one-step procedure: A solution of sodium benzylate in benzyl alcohol prepared from 2.5 g (0.11 mole) of Na in 70 ml of benzyl alcohol was heated to 100°. To this was added dropwise under constant stirring a mixture of 11.7 g (0.1 mole) of phenylacetonitrile, 11.7 g (0.11 mole) of benzaldehyde, 16.5 g (0.11 mole) of benzyl acetate, and 10 ml of benzyl alcohol and the mixture was heated for 50 min. H_2O was added and the oily layer was extracted with ether, dried over K_2CO_3 . After removal of the solvent and excess benzyl alcohol by distillation, the residue was recrystallized from 95% EtOH, the yield of pure α -phenylcinnamonitrile being 17 g (83%), mp 86—87°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2208 ($\text{C}\equiv\text{N}$).

Reduction of α -Phenylcinnamonitrile to α,β -Diphenylpropionitrile by Means of Benzyl Alcohol and Sodium—1.5 g (0.065 mole) of Na was added to 20 ml of benzyl alcohol and the resulting solution was heated to 170°. Under vigorous stirring a mixture of 10.3 g (0.05 mole) of α -phenylcinnamonitrile, 10 g (0.065 mole) of benzyl acetate, and 10 ml of benzyl alcohol was added over a period of 40 to 50 min and the reaction was continued at 170—180° for 2 hr. The resulting mixture was diluted with H_2O and extracted with ether. Ether extract was dried over K_2CO_3 followed by distillation gave 9.8 g (94.7%) of α,β -diphenylpropionitrile, bp 150—156° (4 mmHg). This was proved identical with the authentic sample prepared from phenylacetonitrile and benzyl alcohol in the presence of Na and benzyl acetate with respect to mixed melting point and infrared spectra.

13) A. Meyer, *Chem. Ber.*, 21, 1314 (1888); mp recorded as 133—134°.