Anion Exchange Resins in the Synthesis of Nitriles[1]

M. GORDON,[2a] M. L. DEPAMPHILIS,[2b] AND C. E. GRIFFIN

Department of Chemistry, University of Pittsburgh, Pittsburgh 13, Pennsylvania

Received October 26, 1962

The formation of a number of phenylacetonitriles by reaction of the appropriate benzyl halide with the cyanide form of an anion exchange resin has been achieved in good yield. The reaction can be carried out in a variety of polar and nonpolar solvents. The only anomalous result was obtained with *p*-nitrobenzyl bromide, which underwent condensation to yield 1,2,3-tris(*p*-nitrophenyl)-2-cyanopropane.

The reaction between benzyl halides and alkali metal cyanides in polar solvents constitutes the classical and generally acceptable method for the synthesis of phenylacetonitriles. The polarity and nucleophilicity of the solvent and the basic nature of the cyanide ion do, however, lead to a number of anomalous reactions which limit the utility of the method; ether formation, dehydrohalogenation, allylic rearrangement, and base-catalyzed condensation have been encountered.[3,4] The discovery, in this laboratory,[5] of an anomalous reaction between *o*-phthalimidomethylbenzyl bromide and sodium cyanide in ethanol prompted a search for a new synthetic route to phenylacetonitriles which would avoid any appreciable concentration of cyanide ion in solution and which would be applicable in nonpolar solvents. The demonstration that bromide ion is more strongly held than cyanide ion on strongly basic anion exchange resins[6] coupled with the well known high reactivity of benzyl bromides in displacement reactions suggested an examination of the reaction of the cyanide form of such resins with benzyl bromides. The use of the cyanide form of a resin would satisfy the desired conditions satisfactorily.

Two strongly basic anion exchange resins were converted to their cyanide forms by conventional procedures and allowed to react with five representative benzyl halides. In each case, reaction was successful and the phenylacetonitrile was obtained in good yield. The experimental results of the various studies are summarized in Table I. Three reaction variables were considered in some detail: solvent, reaction time, and reactant-resin ratio. The formation of phenylacetonitrile from benzyl bromide was chosen as the model reaction.

Silver nitrate tests for unchanged halide ion indicated the reaction to be essentially complete in two hours and results of runs 1–6 and 9–12 show that little increase in yield is obtained with an increase of reaction time to three hours. Some loss in yield resulted with longer reaction times (runs 7, 8) and may represent condensation or hydrolysis of the nitrile in the presence of the resin or sorption of the product on the resin. Little change in yield was observed with changes in solvent, with comparable yields being obtained in ethanol, benzene, tetrahydrofuran, ether, and dimethylformamide (runs 1–19). The lack of yield change with increases in solvent polarity indicates that prior ionization of the halide does not occur although the data obtained are not sufficiently accurate to justify further mechanistic speculation. A slight excess of resin over halide led to higher yields than were obtained with a 1:1 ratio; the optimal ratio appears to lie in the range 1.2–1.5. The majority of the experiments employed the cyanide form of Amberlite IRA-400, but four runs (16–19) utilized Dowex 21K; comparable yields were obtained with this resin.

TABLE I

PREPARATION OF NITRILES[a]

Run	Halide	Solvent	Time, hr.	(Equiv. resin)[b]/-(equiv. halide)	Yield, %[c]
1	$C_6H_5CH_2Br$	C_2H_5OH (95%)	1.5	1.0	53
2			2.0	1.0	58
3			2.0	1.2	67
4			3.0	1.2	69
5			2.0	1.5	52
6			3.0	1.5	58
7			1.0	1.72	62
8			4.5	1.72	53
9		C_6H_6	2.0	1.2	72
10			4.0	1.2	72
11			2.5	1.5	63
12			3.0	1.5	60
13		THF	4.0	1.5	70
14			4.0	1.72	66
15		$(C_2H_5)_2O$	4.0	1.5	72
16		C_2H_5OH	4.5	1.72	50
17		C_6H_6	3.5	1.5	58
18		$(C_2H_5)_2O$	4.0	1.5	40
19		DMF	4.5	1.72	50
20	$C_6H_5CH_2Cl$	C_2H_5OH	3.0	1.5	62
21	p-$BrC_6H_4CH_2Br$[d]	C_2H_5OH	2.0	1.0	98
22		C_6H_6	2.5	1.0	31
23	p-$CH_3C_6H_4CH_2Br$	C_2H_5OH	2.0	1.0	43
24	o-$C_6H_4(CH_2Br)_2$	C_2H_5OH	2.0	1.0	83
25	m-$ClC_6H_4CH_2Br$	C_2H_5OH	3.0	1.2	68
26	$CH_2{=}CHCH_2Br$	C_2H_5OH	1.5	1.0	23
27		C_6H_6[e]	3.0	1.2	0
28		C_6H_6	3.0	1.2	5
29		none	3.0	1.0	52

[a] All reactions carried out at 65–75° except for those carried out in ether (35°). [b] Runs 16–19 were carried out with the cyanide ion form of Dowex 21K resin; the remaining runs utilized Amberlite IRA-400. [c] Based on isolated and purified material. [d] Yields in excess of 20% obtained in $(C_2H_5)_2O$, tetrahydrofuran (THF), and dimethylformamide (DMF). [e] Anhydrous solvent.

The yields of nitriles obtained from the five benzyl bromides parallel to a degree the demonstrated relative reactivities of these halides in nucleophilic displace-

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[1] This study was supported in part by a grant (E-16) from the Health Research and Services Foundation, Pittsburgh, Pa. Preliminary communication: M. Gordon and C. E. Griffin, *Chem. Ind.* (London), 1019 (1962).

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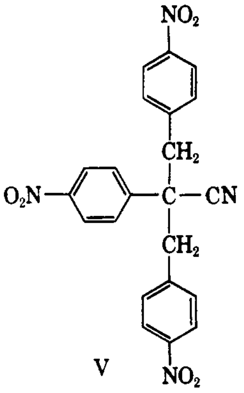
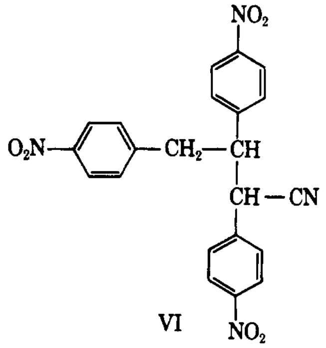
ment reactions.[7,8] This rough dependence, however, suggested an extension of the study to other halides; Streitwieser[7] has indicated that benzyl bromide, benzyl chloride, allyl bromide, and allyl chloride have approximate relative reactivities of 120:120:40:0.8, respectively, in displacement reactions. Using the ion exchange technique, benzyl chloride (run 20) and benzyl bromide (run 6) gave comparable yields,[9] while allyl bromide gave significantly lower yields (runs 26–29, compare 26 and 1) and the reaction failed with allyl chloride; *tert*-butyl bromide also failed to react. Thus, as expected, the effectiveness of this synthetic method reflects the relative reactivities of halides in nucleophilic displacement reactions and the procedure is apparently limited to halides of relatively high reactivity.

The yields obtained by this procedure with benzyl halides are comparable or superior to those obtained by the use of alkali cyanides in polar solvents[7,10]; the restriction to the more highly active halides may suggest a greater selectivity than observed in conventional procedures. As an ion exchange resin reaction, this process is unique; covalent bond breaking and formation, presumably on the surface of the resin, occurs with the anion from the resin becoming covalently bound in the product. Although the formation of covalent bonds occurs in many well known ion exchange processes, the role of the resin in such instances is catalytic. No examples of a process of the type reported here are recorded in the literature; the closest analogy appears to be the conversion of methyl mercuric halides to the hydroxides.[11] Since the difference in affinity of a strongly basic anion exchange resin for bromide and cyanide ions is not great, the general process may be capable of significant extension.

Of the halides examined only *p*-nitrobenzyl bromide (I) led to an unanticipated product; this reaction most clearly illustrates a basic difference in the activity of the cyanide form resin and sodium cyanide in solution. Friedman and Shechter[4] have reported that the reaction of I with sodium cyanide in a variety of solvents leads to the formation of 4,4′-dinitrostilbene (II) rather than the expected *p*-nitrophenylacetonitrile (III). The reaction apparently proceeds through basic attack by cyanide on I to yield the anion followed by alkylation with I. In our hands, reaction of I with the cyanide form of Amberlite IRA-400 in 95% ethanol led to neither of the expected products, II and III, but to a compound (IV) of empirical formula $C_{22}H_{16}N_4O_6$. The infrared spectrum of IV showed characteristic *p*-nitrophenyl absorptions, but was transparent in the nitrile stretching region. This band is also absent in III[12a] and is quite commonly absent in oxygen containing nitriles.[12b] The presence of the nitrile function was confirmed by hydrolysis to a carboxylic acid. This reaction required stringent conditions of the type employed by Hauser[13] for the hydrolysis of α,α-dibenzylphenylacetonitriles, indicating that IV possessed α-branching. The ultraviolet absorption spectrum (λ_{max} = 267 mμ, $\epsilon = 3.05 \times 10^4$) indicated the presence of three isolated *p*-nitrophenyl chromophores (nitrobenzene,[14] λ_{max} = 268.5 mμ, $\epsilon = 7.8 \times 10^3$; *p*-nitrotoluene,[15] λ_{max} = 274 mμ, $\epsilon = 9.3 \times 10^3$). Two isomeric structures, V and VI, for IV are consistent with this information and probable reaction paths. Differentiation between the two structures was provided by an examination of the proton magnetic resonance spectrum of IV.[16] In addition to aromatic signals at τ = 1.85–2.65, a single, unsplit methylenic absorption was observed at τ = 6.24. The methylene protons of phenylacetonitrile give an unsplit absorption at τ = 6.28. Since structure VI should yield complex methylenic absorptions, compound IV is identified as 1,2,3-tris(*p*-nitrophenyl)-2-cyanopropane (V). V could readily arise by reaction of I with the resin to yield the simple nitrile (III) which could be converted to its anion by the resin and alkylated with I to yield α,β-di(*p*-nitrophenyl)propionitrile; repetition of anion formation and alkylation would lead to V.[17] Thus, the basic catalytic activity of the cyanide form of the resin and sodium cyanide in solution differ markedly, with the latter being more basic, *i.e.*, capable of converting the benzyl halide (I) to its anion.


V


VI

Experimental[18]

Preparation of the Resin.—Amberlite IRA-400 or Dowex 21K (chloride ion form) was washed several times with distilled water to remove foreign material and then washed three times with three times its volume of 20% aqueous sodium cyanide. The mixture of resin and cyanide solution was stirred for 5 min., diluted with distilled water (0.5 volume) and stirred for an additional 5 min. The cyanide solution was decanted each time and the resin was finally washed with distilled water until the supernatant liquid gave a negative cyanide test (silver nitrate). The water was then decanted and replaced by the solvent to be em-

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(8) The lack of a direct dependence is not surprising and may result from a number of factors: the unsatisfactory nature of isolated yields of product as a reactivity criteria; uninvestigated resin variables such as sorptive behavior, surface wetting, thickness of stationary surface film, resin pore size, etc.; and the fact that the data cited by Streitwieser[7] are based on reactions of halides with solvated nucleophiles rather than resins. We are indebted to the referee for suggesting the factor of resin variables.

(9) While the formation of phenylacetonitrile in good yield from benzyl chloride was anticipated on the basis of halide reactivity, the result was unexpected since resins of the type employed have a lower affinity for chloride than for cyanide ion.[6]

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(15) W. M. Schubert, J. Robins, and J. L. Haun, *ibid.*, **79**, 910 (1957).

(16) We are indebted to Dr. B. L. Shapiro for the determination and interpretation of the n.m.r. spectrum of IV.

(17) Similar bis-alkylations of phenylacetonitriles are well known; *cf.* ref. 13 and M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).

(18) All melting points are uncorrected. Ultraviolet, infrared, and n.m.r. spectra were obtained on Cary Model 14, Perkin-Elmer Model 21 and Varian A 60 spectrometers.

ployed as reaction medium. After reaction with a halide, the resin could be regenerated by the same procedure; some mechanical deterioration of the resin occurred on stirring limiting its use to three nitrile preparations. One milliliter of wet resin was taken as one milliequivalent of cyanide ion.

General Procedure for the Preparation of Nitriles.—The general procedure is illustrated by the preparation of phenylacetonitrile (run 1, Table I). A mixture of 8.6 g. of benzyl bromide (0.05 mole) in 100 ml. of 95% ethanol and 50 ml. of Amberlite IRA-400 (cyanide form) (0.05 equiv.) was stirred for 1.5 hr. in a 300-ml. erlenmeyer flask. The temperature of the reaction mixture was maintained at 65° by means of a heating tape wound around the flask; continual stirring was provided by a magnetic stirrer. The extent of reaction could be followed conveniently by testing the supernatant liquid with silver nitrate solution. The resin was removed by filtration and washed with five 10-ml. portions of ethanol; the combined filtrates were concentrated under reduced pressure and then distilled to give 3.1 g. of phenylacetonitrile (53%), b.p. 110–111°/15 mm., $n^{27}\text{D}$ 1.5201 (lit. b.p. 107°/12 mm.,[19] $n^{25}\text{D}$ 1.5211[20]). The infrared spectrum of the compound was identical with that of an authentic sample.

The other nitriles prepared in this study had the following physical constants: *p*-tolylaceto-, b.p. 239–241° (lit.,[21] b.p. 242–243°); *p*-bromophenylaceto-, m.p. 47–48° (lit.,[22] m.p. 46–47°); *m*-chlorophenylaceto-, b.p. 153–155°/26 mm. (lit.,[23] b.p. 134–136°/10 mm.); *o*-phenylenediaceto-, m.p. 59–60° (lit.,[24] m.p. 60°); allyl cyanide, b.p. 116–118° (lit.,[25] b.p. 114–116°). All of the above compounds showed the expected infrared spectra and in all cases exhibited nitrile stretching bands.

All of the starting halides were commercial products and were redistilled or recrystallized prior to use.

1,2,3-Tris(*p*-nitrophenyl)-2-cyanopropane (IV or V).—The addition of 50 ml. of Amberlite IRA-400 (cyanide form) to a solution of 10.8 g. of *p*-nitrobenzyl bromide (0.05 mole) in 100 ml. of ethanol gave a bright red solution immediately; the resin turned black. The mixture was stirred at 70° for 1 hr., filtered, and the resin was washed with ethanol and ether. The resin was then washed with several portions of acetone; concentration of the acetone washings gave 1.6 g. (36%) of tan needles, m.p. 202–204°, which were recrystallized from aqueous acetone to give colorless crystals of IV, m.p. 204–204.5°.

Anal. Calcd. for $C_{22}H_{16}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.34, 61.18; H, 3.77, 3.71; N, 13.52, 13.69.

The infrared spectrum (Nujol mull) of this material showed typical *p*-nitrophenyl (857.6, 1603, 1613) and nitro (1348, 1538 cm.$^{-1}$) absorptions; a maximum at 267 mμ (log ϵ = 4.48) was observed in the ultraviolet (95% ethanol). The n.m.r. spectrum in deuteroacetone showed peaks at τ = 1.85, 2.00, 2.15, 2.28, 2.50, 2.65, and 6.24. Additional quantities of IV could be isolated from the original ethanol solution and washings by dilution with water.

The tris compound (IV) was hydrolyzed by heating with sulfuric acid and sodium chloride at 190° for 1 hr.; after cooling the solution was poured over ice to give a colorless precipitate. Recrystallization of the precipitate from aqueous acetone gave colorless crystals, m.p. 231.5–234°. The product was insoluble in chloroform, acetonitrile, carbon tetrachloride, water, and 10% sodium hydroxide. The infrared spectrum (Nujol mull) showed typical strong carboxyl (1310, 1690) and nitro (1350, 1515 cm.$^{-1}$) absorptions.

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On the Palladium-catalyzed Hydrogenolysis of the Epoxysuccinic Acids[1]

OSCAR GAWRON, THOMAS P. FONDY, AND DONALD J. PARKER

Department of Chemistry, Duquesne University, Pittsburgh 19, Pennsylvania

Received October 9, 1962

The hydrogenolysis of *cis*-epoxysuccinic acid and *trans*-epoxysuccinic acid in aqueous solution with palladium-on-charcoal catalyst leads to the formation of malic acid, succinic acid, and diglycolic acid. Hydrogenolysis of the epoxides to malic acid proceeds in a *trans* fashion, *threo*-3-deuterio-DL-malic acid and *erythro*-3-deuterio-DL-malic acid resulting from *cis*-epoxysuccinic acid and *trans*-epoxysuccinic acid, respectively. Mixed *erythro*- and *threo*-2,3-dideuteriosuccinic acids result from *cis*-epoxysuccinic acid and *threo*-2,3-dideuteriosuccinic acid results from *trans*-epoxysuccinic acid. Malic acid is not an intermediate for the formation of succinic acid.

The hydrogenolysis of the epoxysuccinic acids has been under investigation in this laboratory and it has been noted[2] in a preliminary fashion that the hydrogenolysis of *cis*-epoxysuccinic acid in 9:1 dioxane–deuterium oxide with deuterium yields *threo*-DL-3-deuteriomalic acid, opening of the epoxide ring with inversion having taken place. In this paper further results on the identity and steric configuration of the products obtained by hydrogenolysis of the epoxysuccinic acids are reported. Interest in these hydrogenolyses stems from the fact that the products (with deuterium), *threo*-DL-3-deuteriomalic acid, mixed *erythro*- and *threo*-2,3-dideuteriosuccinic acids and diglycolic acid from *cis*-epoxysuccinic acid and *erythro*-DL-3-deuteriomalic acid, *threo*-2,3-dideuteriosuccinic acid and diglycolic acid from *trans*-DL-epoxysuccinic acid are pertinent to mechanisms of hydrogenolysis of epoxides.[3,4] Of further interest, these hydrogenolyses provide a convenient synthetic route to *threo*- and *erythro*-3-deuterio-DL-malic acids and the *threo*- and *erythro*-3-deuterio-DL-chlorosuccinic acids which may be obtained from the malic acids. These four acids provide convenient substrates for studying the stereochemistry of enzymatic and non-enzymatic dehydrations,[2] dehydrochlorinations,[5] and dehydrogenations.[5]

Experimental

General Procedure for Hydrogenolysis.—Hydrogenolyses were carried out at room temperature in the usual Paar apparatus. For small scale (1–2 mmoles) exploratory experiments, the tank was replaced by a small section of appropriately threaded pipe and small glass bottles were used as the reaction vessels. With these modifications, the dead air space was approximately 50 ml. Small scale hydrogenations at atmospheric pressure were carried out in a three-necked, 100-ml. flask equipped with a pressure-equalizing dropping funnel and a magnetic stirrer and connected to a gas buret containing dibutyl phthalate. For hydrogenations with deuterium, Volk Radiochemical Co. 99.7% deuterium gas (500 p.s.i.) was used and as required 99.9% deuterium oxide from Bio-Rad Laboratories. The catalyst used for all runs was

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