TABLE III
MEAN CONDUCTIMETRIC SOLVOLYSIS RATES OF 1-*tert*-BUTYL-3-AZETIDINYL TOSYLATE

Solvent	Temp, °C	Rate, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
MeOH	30.0	$(9.09 \pm 0.39) \times 10^{-5}$		
MeOH + Et_3N[a]	30.0	$(9.00 \pm 0.17) \times 10^{-5}$	25.3 ± 1	6.3[b]
	40.0	$(3.38 \pm 0.03) \times 10^{-4}$		
	50.0	$(1.29 \pm 0.07) \times 10^{-3}$		
50% aqueous acetone	15.0	$(4.88 \pm 0.10) \times 10^{-5}$	22.8 ± 0.5	0.8
	30.0	$(3.61 \pm 0.08) \times 10^{-4}$		
	45.5	$(2.42 \pm 0.05) \times 10^{-3}$		
60% aqueous acetone	15.0	$(3.49 \pm 0.14) \times 10^{-5}$	22.05 ± 1	2.2[b]
	30.0	$(2.69 \pm 0.11) \times 10^{-4}$		
	45.5	$(1.55 \pm 0.03) \times 10^{-3}$		

[a] Contains a tenfold excess of triethylamine. [b] In view of the rather large variance in $\Delta H^{\pm}$, $\Delta S^{\pm}$ is probably valid to only ±3 eu.

solvolyses of the carbocyclic (**3a**,**b**) and heterocyclic (**1a**) tosylates are very similar in 60% aqueous acetone, and that the rate increase observed in the solvolysis of **1a** relative to **3a–c** is primarily due to $\Delta S^{\pm}$.

It is interesting that the enthalpies of activation for these tosylates compare so favorably. The enthalpy of activation for the solvolysis of **1a** may be the result of a delicate balance of inductive electron withdrawal from the cationic site by the nitrogen atom and stabilization of the cation by charge dispersal to the nitrogen atom by anchimeric assistance.[11] It seems fortuitous that $\Delta H^{\pm}$ for the solvolysis of **1a** and of **3a** or **3b** are identical, within experimental error, particularly in view of the uncertainty[12] surrounding the nature of the intermediate in the solvolysis of cyclobutyl tosylates.

The large values of $\Delta S^{\pm}$ observed in the solvolysis reactions of **1a** may be interpreted as additional support for an ionic intermediate.[13] Indeed, one is tempted to argue that the value of $\Delta S^{\pm}$ (in 60% aqueous acetone), relative to **3a–c**, is indicative of the significance of anchimeric assistance[14] by the nitrogen atom *in the transition state* involved in the solvolysis of **1a**.

The effects of substitution of C-2 on the solvolysis rates and product distribution are presently being pursued. The results of this study may give a more definitive insight into the nature of the N–C-3 bond.

Experimental Section

1-*tert*-Butyl-3-azetidinyl Tosylate (1a).—The synthesis of this compound has been described.[8]

Absolute Methanol.—Commercial absolute methanol was further dried by distillation from magnesium methoxide.[15]

Relative Basicities.—Absolute pK_a values were not determined (the null point of the pH meter being arbitrarily set at 7.07 and 7.00 for solvent at 25 and 36.25°, respectively).

The "basicity constants" of **1d** (in methanol) and **1e** (in 60% aqueous acetone) were determined by recording the "pH" of a solution of the azetidine while hydrogen chloride, in the appropriate solvent, was added at constant rate. The "pK_a" is the "pH" at the half-equivalence point.

The "basicity" constants of **1a** were determined by dissolving 1 equiv of **1a** in a solution of the appropriate solvent containing 0.5 equiv of anhydrous *p*-toluenesulfonic acid and immediately determining the "pH."

Method of Determining Remaining Cyanide.—Aliquots (5 ml) of the methanolic reaction mixture were added to *ca.* 30 ml of ice water. The resulting solution was covered with *ca.* 10 ml of ether and titrated with 0.05–0.1 *N* silver nitrate solutions (the volumes being recorded to 0.001 ml). The reaction with cyanide was followed through *ca.* one half-life; the solvolysis reactions were followed for 4–10 half-lives.

Registry No.—**1a**, 17358-65-5; methanol, 67-56-1; potassium cyanide, 151-50-8; acetone, 67-64-1; triethylamine, 121-44-8.

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(11) We have no evidence for participation of nonclassical ions in the solvolysis of **1a**.

(12) See, for example, R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959); R. E. Davis and A. Ohno, *Tetrahedron*, 2063 (1968).

(13) E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958); S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); D. J. Cram, *ibid.*, **86**, 3767 (1964).

(14) Anchimeric assistance, *via* phenonium ions, seems to increase the value of $\Delta S^{\pm}$. See the data of C. J. Kim and H. C. Brown, *ibid.*, **91**, 4287 (1969); **91**, 4289 (1969); C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291 (1969).

(15) A. I. Vogel, "A Text-Book of Practical Organic Chemistry, 3rd ed, Wiley, New York, N. Y., 1957, p 169.

C-Alkylation of Active Methylene Compounds by Means of Alcohols. VII.[1] Synthesis of α-Substituted Phenylacetonitriles from α-Phenylacetoacetonitrile

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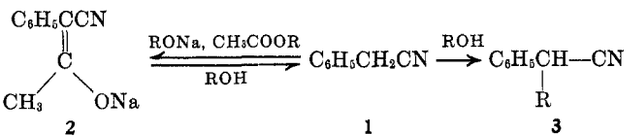
In a preceding paper of this series we have reported that phenylacetonitrile **1** is readily alkylated by means of four to five times the calculated amount of alcohols in the presence of metallic sodium and appropriate ester to give α-substituted phenylacetonitrile **3**. Having demonstrated that the alkylation proceeds *via* α-phenylacetoacetonitrile sodium salt **2** (Scheme I, **1** → **2** → **1** → **3**), we now wished to study the possibility that the reaction starting with **2** might be of general application for the preparation of α-substituted phenylacetonitrile **3**. By simply heating a mixture of **2** and alcohol, a series of α-substituted phenylacetonitrile

(1) Paper VI: S. Miyano and N. Abe, *J. Org. Chem.*, **36**, 2948 (1971).

(2) To whom inquiries should be sent.

SCHEME I



was obtained in excellent yields and this route of preparation is now established.

As compared with the previous method[1] the procedure was thus simplified considerably, since the use of sodium and appropriate acetic ester was not required.

Our results are summarized in Tables I and II. Obviously **2** underwent alcoholysis to give **1** which, in turn, was alkylated to give **3** as a final product.

TABLE I

ALKYLATION BY LOWER ALIPHATIC AND ALICYCLIC ALCOHOLS (PROCEDURE A)

Expt	Registry no.	Alcohol	Product: Bp (18 mm) or mp, °C	Product: Yield, %[a]
1	769-68-6	Ethyl	120–123	62.1
2	5558-78-1	*n*-Propyl	132–135	76.1
3	3508-98-3	*n*-Butyl	140–145	79.2
4	5558-31-6	Isobutyl	134–138	78.0
5	5558-33-8	*n*-Amyl	149–154	81.8
6	5558-34-9	Isoamyl	143–149	79.7
7[b]	3753-59-1	Cyclopentyl	44–45[c]	33.5
8[b]	3893-23-0	Cyclohexyl	54–56[d]	47.2

[a] Based on phenylacetoacetonitrile sodium salt **2**. [b] Heated at 230–240° for 2 hr. [c] A fraction boiling at 125–135° (2 mm) solidified on cooling, and was recrystallized from petroleum ether (bp 30–60°) as colorless needles, literature mp 50°: G. Vasiliu, V. Pumitoroscu, and H. Valcan, *Bul. Soc. Chim. România Stiinte, Bul. Stiinte Fiz.*, **2**, 3A, 54 (1941). *Anal.* Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.29; H, 8.23; N, 7.42. [d] Colorless needles from petroleum ether.

In the alkylations with lower alcohols (from ethyl to amyl) the procedure consists in heating the reaction mixture at 210–220° in an autoclave for 1 hr (procedure A). Yields are slightly improved over those of the method starting with phenylacetonitrile (Table I). However, in the alkylations with secondary alcohols such as isopropyl, *sec*-butyl, cyclopentyl, and cyclohexyl alcohols the products were contaminated with α-alkylidenephenylacetonitrile, which is an intermediate in the alkylation sequence,[1] and isolation by fractional distillation proved difficult. Only α-cyclopentylphenylacetonitrile and cyclohexylphenylacetonitrile, which can be crystallized out from the distillate, were secured.

With higher alcohols (higher than *n*-heptyl) that do not require an autoclave the procedure is extremely simple: when a mixed slurry of **2** and 1.5 times the calculated amount of alcohol was maintained at 210° for a few minutes a vigorous reaction was induced and the subsequent heating brought the overall reaction into completion in a surprisingly short period, approximately 30 min (procedure B). Yields are excellent and comparable to those of the previous method (Table II).

Alkylations with *n*-hexyl and 2-ethylhexyl alcohols are two exceptions: 30-min heating of the reactants failed, only starting nitrile being recovered, presumably because of the low boiling point of the former and steric hindrance involved in the latter, respectively.

TABLE II

ALKYLATION BY HIGHER ALIPHATIC AND ARALKYL ALCOHOLS (PROCEDURE B)

Expt	Registry no.	R	Product: Bp (2 mm) or mp, °C	Product: Yield, %[a]
9[b]	5558-35-0	*n*-Hexyl	127–130	70.6
10	5558-36-1	*n*-Heptyl	138–145	69.8
11	15601-30-6	*n*-Octyl	147–151	82.1
12[b]	17178-81-3	2-Ethylhexyl	136–141	70.5
13	17179-16-7	*n*-Nonyl	151–162	79.0
14	30889-57-7	3,5,5-Trimethylhexyl	140–144	75.7
15	17179-17-8	*n*-Decyl	174–180	74.7
16	17179-18-9	Lauryl	191–194	71.6
17	3333-14-0	Benzyl	56–57[c,d]	62.8
18	32970-77-7	4-Methylbenzyl	58–59[c,e]	67.0
19	32970-78-8	4-Anisyl	86–87[c,f]	54.0
20	32970-79-9	4-Chlorobenzyl	109.5–110.5[c,g]	67.9
21	32970-47-1	3,4-Dimethoxybenzyl	94–95.5[c,h]	59.2
22		3,4-Methylenedioxybenzyl	73–74[c,i]	32.7
23	6443-81-8	3-Phenyl-1-propyl	76–77[c,j]	70.6

[a] Based on phenylacetoacetonitrile sodium salt **2**. [b] Since the alkylation failed according to procedure B, a mixture of 0.1 mol of phenylacetoacetonitrile sodium salt and 0.3 mol of alcohol was heated for 3 hr. [c] Melting point. [d] Colorless needles (from ethanol). [e] Colorless platelets (from methanol), literature mp 58°: M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 493 (1958). *Anal.* Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.50; H, 6.86; N, 6.52. [f] Colorless platelets (from ethanol), literature mp 86–87°: H. Lettré, W. Haede, and L. Schäfer, *Hoppe-Seyler's Z. Physiol. Chem.*, **289**, 298 (1952). *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.29; N, 5.96. [g] Colorless platelets (from ethanol), literature mp 113–114°: M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 493 (1958). *Anal.* Calcd for $C_{15}H_{12}NCl$: C, 74.53; H, 5.00; N, 5.80. Found: C, 74.85; H, 5.19; N, 5.54. [h] Colorless needles (from methanol), literature mp 98°: P. C. Jocelyn, *J. Chem. Soc.*, 1640 (1954). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 75.98; H, 6.22; N, 5.34. [i] Colorless prisms (from methanol). No depression of melting point on admixture with authentic sample was observed. [j] Colorless prisms (from methanol), literature mp 79°: W. Borsche, *Ber.*, **45**, 624 (1912). *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.38; H, 7.18; N, 6.01.

However, satisfactory results were obtained when the amount of alcohol was doubled and the reaction period was extended to 3 hr (Table II, expt 9 and 12). According to procedure B alkylations by means of a series of aralkyl alcohols were also successfully achieved (Table II).

In view of the fact that the previous method[1] becomes less attractive for large-scale operation due to the quantities of alcohol that must be employed, it is noteworthy that smaller amount of alcohols; *i.e.*, 1.5 and 3 times the calculated amount of alcohol in alkylations with higher alcohols (procedure B) and with lower alcohols (procedure A), respectively, is required as compared with 4–5 times the calculated amount in the previous method.

Since phenylacetoacetonitrile sodium salt **2** can be readily prepared by condensation between phenylacetonitrile and ethyl acetate in the presence of sodium ethoxide[3] and shows good shelf stability, the present method offers advantage sufficient to compensate for time and cost of producing **2**. Thus, the described procedure features low price of the reagents employed and very simple manipulation, and is possibly the most convenient method for the preparation of α-substituted phenylacetonitriles.

(3) P. L. Julian, J. J. Oliver, R. H. Kimball, A. B. Pike, and G. D. Jefferson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957, p 487.

Experimental Section

Alkylation with Lower Aliphatic and Alicyclic Alcohols (Procedure A) (Table I, Experiment 1–8).—A mixture of 0.1 mol of **2** and 0.3 mol of alcohol was heated with stirring in an autoclave at 210–220° for 1 hr. Water was added to the content of the autoclave, the resulting suspension was stirred, and the upper clear layer was removed by decantation from the precipitated sodium acetate hydrate. Removal of excess alcohol and ether by distillation gave light brown residual oil which was dissolved in ether. The ethereal solution was washed with several portions of water until the solution became clear, and the ethereal layer was dried (K_2CO_3), concentrated, and distilled, giving α-alkyl phenylacetonitrile.

Akylation with Higher Aliphatic Alcohols (Procedure B), (Table II, Experiment 9–16).—A mixed slurry of 0.05 mol of **2** and 0.075 mol of alcohol was heated at 210° for a few minutes when a vigorous reaction started. This was heated at 210–220° for 30 min. After cooling, water was added to the brownish-yellow cake, the resulting oily layer was extracted with ether, and the ethereal layer was washed with water, dried (K_2CO_3), concentrated, and distilled, giving α-alkylphenylacetonitrile.

Alkylation with Aralkyl Alcohols (Procedure B) (Table II, Experiment 17–23).—A mixed slurry of 0.05 mol of **2** and 0.075 mol of aralkyl alcohol was heated at 200–210° for 20 min. After cooling, water was added to the brownish-yellow cake. The resulting oily layer was extracted with ether, and the ethereal layer was washed with water, dried (K_2CO_3), concentrated, and distilled, giving α-aralkylphenylacetonitrile. The product, which solidified on cooling, was recrystallized from methanol or ethanol. In two cases, expt 20 and 21, crude products were directly obtained as crystals when water was added to the mixture after the reaction was complete.

Registry No.—**2**, 32970-68-6.

Proton Magnetic Resonance and Chemical Evidence for Stereospecificity in the Reaction of *cis*- and *trans*-1-Phenyl-4-*tert*-butylcyclohexanol with HCl. Proton Magnetic Resonance Analysis of the Reaction of Several Substituted 1-Arylcyclohexyl Systems with HCl and FSO_3H–SbF_5–SO_2

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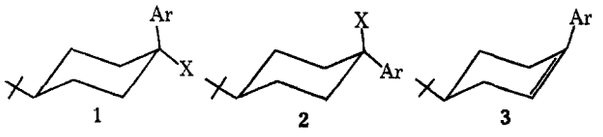
The isolation of stereoisomers from the addition of HX to cyclohexenes[1] or other cycloalkenes[2] has been reported only rarely. To our knowledge, the identification and isolation of similar stereoisomers from substituted cyclohexanols has not been recorded. We selected alcohols *cis*-**1a**, *cis*-**1b**, *trans*-**2a**, and *trans*-**2b** for the study with HCl since the stereomeric chlorides *cis*-**1c** and *trans*-**2c** have been characterized.[1]



	X	Ar
a	OH	C_6H_5
b	OH	p-$CH_3OC_6H_4$
c	Cl	C_6H_5
d	Cl	p-$CH_3OC_6H_4$

a, Ar = C_6H_5

b, Ar = p-$CH_3OC_6H_4$

We have now found that alcohols *cis*-**1a** and *trans*-**2a**[3] react in a stereospecific fashion with HCl(g). Suspended in anhydrous pentane at −30° under N_2, *cis*-**1a** was treated with anhydrous HCl(g) and gave (after 45 min) a ratio of 3.67:1 for the chlorides *cis*-**1c**:*trans*-**2c** as measured from peak areas for the corresponding *tert*-butyl protons (δ 0.74 and 0.92, respectively) in the pmr spectrum of the reaction mixture. These peaks are clearly separated in $DCCl_3$ at 50-Hz sweep width. The complete disappearance of a signal for the proton on oxygen suggested a nearly quantitative conversion of

$$\textit{cis}\text{-}\mathbf{1a} + HCl \xrightarrow[-30°]{\text{pentane}} \underset{(78.6\%)}{\textit{cis}\text{-}\mathbf{1c}} + \underset{(21.4\%)}{\textit{trans}\text{-}\mathbf{2c}}$$

$$\textit{trans}\text{-}\mathbf{2a} + HCl \xrightarrow[-30°]{\text{pentane}} \underset{(19.4\%)}{\textit{cis}\text{-}\mathbf{1c}} + \underset{(80.6\%)}{\textit{trans}\text{-}\mathbf{2c}}$$

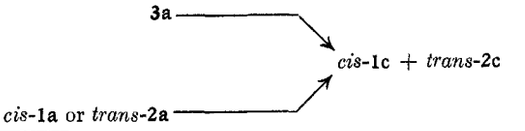
alcohol *cis*-**1a**. The overall phenomenon is surprising in view of the predominance of the chloride *cis*-**2c** at short reaction times (*ca.* 15 min) when **3a** was treated with HCl at −70°.[1] A check on the reaction of *cis*-**1a** at −70° after 45 min did *not* reveal a significant change in the ratio of products (Table I). In contrast, if **3a** was allowed to react with HCl for 45 min, no starting material could be detected in the mixture by pmr, and *cis*-**1c**:*trans*-**2c** was 1.0:2.06. Since the ratio *cis*-**1a**:**3a** in the two separate experiments was only 1.3:1, these above data can be compared, all other reaction conditions being identical. It should be noted (Table I), of course, that there is a dependence of [*cis*-**1c**]:[*trans*-**2c**] upon the initial concentration of **3a** as expected for the same period of time. A similar dependence upon rate of addition of HCl to **3a** was reported.[1]

TABLE I

Compd	Temp, °C	*cis*-**1c**, %	*trans*-**2c**, %	Time, min
cis-**1a** (alcohol)	−30	78.6	21.4	45
(0.0017 mol)[a]	−70	78.6	21.4	45
trans-**2a** (alcohol)	−30	19.4	80.6	45
(0.0022 mol)[a]	−70	28.2	71.8	45
3a (alkene)	−70	48.6	20.5	15[b]
(0.0013 mol)[a]	−70	32.3	67.7	45
3a (alkene)	−70	79.1	20.9	15
(0.0037 mol)[a]	−70	71.8	28.2	45

[a] Per 100 ml of *n*-pentane. [b] Unreacted **3a** detected was 30.9%.

It appears that no common intermediate is formed from the reaction of HCl with either **3a** *or* **1a** *(or* **2a***) in pentane at −70°.* Therefore the mechanisms differ. To our knowledge, this is the first report of the reaction of HCl



(1) K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *Chem. Commun.*, 1246 (1970).

(2) P. K. Freeman, F. A. Raymond, and M. F. Raymond, *J. Org. Chem.*, **32**, 24 (1967).

(3) The alcohols were of purity greater than 99.5% by glc analysis. Although the preparation [E. W. Garbisch, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963)] and purification technique [G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. C*, 1106 (1968)] are reported, modification of procedures afforded more pure products in a simpler process; see R. O. Lyerla, Ph.D. Dissertation, Oklahoma State University, 1970.