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Phenylacetonitrile can be condensed with *N*-substituted-bis(2-chloroethyl)amines in aqueous sodium hydroxide solution to produce *N*-substituted-4-cyano-4-phenylpiperidines. Hexadecyltributylphosphonium bromide is an effective catalyst for this phase-transfer reaction.

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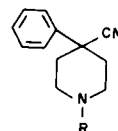
Members of the *N*-substituted-4-cyano-4-phenylpiperidine family have great medicinal importance because many possess good antispasmodic or anesthetic properties. They are also important intermediates in the synthesis of meperidine(4-carboxyl) and ketobemidone(4-acyl) derivatives which have high analgesic potencies

The first general synthesis of these compounds was reported by Eisleb (1) and consisted of refluxing a mixture of phenylacetonitrile, an *N*-alkyl-bis(2-chloroethyl)amine, sodium amide, and toluene for one hour. Isolated yields of 57-67% were reported. Phenylacetonitrile has also been dialkylated under the influence of sodium amide to product  $\alpha,\alpha$ -bis(2-dimethylaminoethyl)phenylacetonitrile which in turn can be converted into the 1,1-dimethylpiperidinium salt by cyanogen bromide (2) or into *N*-methyl-4-cyano-4-phenylpiperidine by thermolysis (3).

The recent advent of phase-transfer catalysis has provided attractive alternatives to the use of hazardous bases such as sodium amide and anhydrous aprotic solvents. It has been demonstrated that phenylacetonitrile can be alkylated under phase-transfer conditions with 1,5-dibromopentane and bis(2-chloroethyl)ether to yield the corresponding six-membered rings (4). Attempts to extend this technique to the synthesis of nitrogen heterocycles have been plagued by very low yields (5,6).

While attempting to prepare some piperidine derivatives by phase-transfer methods, we compared the activity of a number of catalysts including benzyltriethylammonium chloride, tricaprilmethylammonium chloride (Aliquat 336), trialkyl(C<sub>8</sub>-C<sub>10</sub>)methylammonium chloride (Adogen 464), dicyclohexyl-18-crown-6, and hexadecyltributylphosphonium bromide. All of these catalysts are active, but the phosphonium catalyst is vastly superior to the others for this specific application. It produces high yields of the desired compounds in a short reaction time with only trace amounts of undesired byproducts being formed. Typically a mixture of phenylacetonitrile, an *N*-substituted-bis(2-chloroethyl)-amine, 50% aqueous sodium hydroxide solution, and a catalytic amount of hexadecyltributylphosphonium bromide is stirred and heated at 100° for one hour. Isolated yields of the *N*-substituted-4-cyano-4-phenylpiperidines range from 60-88% (Table I). A variety

Table I  
Synthesis of *N*-Substituted-4-cyano-4-phenylpiperidines



R	% Yield	mp, °C	bp, °C	Reference
Me	72	50°	138°/2.5 mm	(1)
Et	71	—	143°/2.5 mm	(7)
<i>n</i> -Bu	65	—	155°/2.5 mm	(5)
<i>iso</i> -Bu	60	—	153°/2.5 mm	(a)
<i>t</i> -Bu	82	106°	—	(b)
Benzyl	87	75°	—	(1)
Phenyl	88	95°	—	(8)

(a) *Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>: C, 79.27; H, 9.17; N, 11.56. Found: C, 79.09; H, 9.34; N, 11.45. (b) *Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>: C, 79.27; H, 9.17; N, 11.56. Found: C, 79.26; H, 9.17; N, 11.39.



of substituents can be tolerated on the nitrogen atom including those (phenyl, *t*-butyl) which could not have been incorporated into the molecule by direct alkylation reactions.

In summary, this method provides an attractive alternative to the reactions utilizing sodium amide in that sodium hydroxide is the base and water is the reaction medium. Reaction conditions are mild, times are short, and yields are generally higher than those reported when sodium amide is used.

#### EXPERIMENTAL

The <sup>1</sup>H-nmr spectra were recorded on a Perkin-Elmer R-12B spectrometer utilizing carbon tetrachloride as the solvent. Chemical shifts are reported in ppm from TMS as an internal standard and are given in  $\delta$  units. All products in Table II had ir absorptions for the cyano group at

Table II  
Spectral Properties of *N*-Substituted-4-cyano-4-phenylpiperidines  
NMR ( $\delta$ )

R		<i>N</i> -Substituent	
Me	7.52 (m, 5H)	2.44 (s, 3H)	1.9-3.1 (m, 8H)
Et	7.38 (m, 5H)	1.10 (t, 3H), 2.51 (q, 2H)	2.0-3.2 (m, 8H)
<i>n</i> -Bu	7.36 (m, 5H)	0.93 (t, 3H), 1.45 (m, 4H) 2.45 (t, 2H)	2.0-3.3 (m, 8H)
<i>iso</i> -Bu	7.35 (m, 5H)	0.85 (d, 6H), 1.70 (m, 1H) 2.20 (d, 2H)	1.9-3.1 (m, 8H)
<i>t</i> -Bu	7.35 (m, 5H)	1.10 (s, 9H)	2.0-3.2 (m, 8H)
Benzyl	7.37 (m, 5H)	3.57 (s, 2H), 7.24 (s, 5H)	2.05 (m, 4H), 2.80 (m, 4H)
Phenyl	7.35 (m, 5H)	7.00 (m, 5H)	2.0-3.1 (m, 8H)

approximately 2245  $\text{cm}^{-1}$  and absorptions for the phenyl group at approximately 695 and 760  $\text{cm}^{-1}$ . Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

The *N*-substituted-bis(2-chloroethyl)amines and their hydrochloride salts were prepared according to literature procedures (1,8,9). The phosphonium catalyst was prepared from 1-bromohexadecane and tributylphosphine (10). The following is a typical procedure.

#### *N*-Phenyl-4-cyano-4-phenylpiperidine.

Into a three-necked, 100-ml round bottom flask equipped with a mechanical stirrer and a reflux condenser was placed 3.00 g (25.6 mmoles) of phenylacetonitrile, 5.58 g (25.6 mmoles) of *N*-phenyl-bis(2-chloroethyl)amine (or an equivalent amount of the hydrochloride salt), 0.67 g (1.3 mmoles) of hexadecyltributylphosphonium bromide and 30 ml of 50% aqueous sodium hydroxide. The mixture was stirred vigorously while being heated at 100° for one hour. The cooled mixture was transferred to a separatory funnel, diluted with 100 ml water and extracted with ether (3  $\times$  50 ml). The ether extracts were washed with water (2  $\times$  50 ml) and extracted with three 50 ml portions of a 1:1 mixture of concentrated hydrochloric acid and water. The acid extracts were neutralized with solid sodium carbonate and extracted with ether (3  $\times$  50 ml). The

ether extracts were dried over anhydrous magnesium sulfate and evaporated to yield 5.92 g (88%) of the desired compound, mp 94-95° (lit (8) 97°).

#### Acknowledgement.

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