Synthesis of Isonitriles[1]

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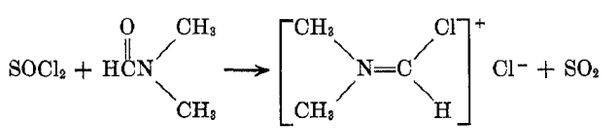
A convenient synthesis of isonitriles has been devised using a *N,N*-dimethylformamide (DMF) solution of chlorodimethylformiminium chloride, prepared *in situ* from thionyl chloride and DMF, to dehydrate a variety of formamides. This general procedure enables one to prepare aliphatic, alicyclic, vinylic, and aromatic isonitriles in excellent yields. The reduction of isocyanates with lithium tri-*tert*-butoxylaluminum hydride to yield formamides is described.

Of the many methods available for the preparation of isonitriles,[2] those that appear to have the most general application involve the reaction of alkyl halides with heavy metal cyanide salts,[3] the addition of dichlorocarbene to amines, the reduction of isocyanates and isothiocyanates,[4] the copper-catalyzed addition of hydrogen cyanide to tertiary olefins,[5] and the dehydration of formamides.[6] This final method has provided the most convenient approach using reagents such as tosyl chloride,[6,7] phosphorus oxychloride,[8] cyanuryl chloride,[9] and triphenylphosphine–carbon tetrachloride[10] to effect the dehydration. By far the most preferred dehydrating procedure is that of Ugi,[2,11] who used phosgene in the presence of a tertiary amine.

To circumvent the use of phosgene, chlorodimethylformiminium chloride[12] (1) (Vilsmeier reagent[13]) was selected as a possible dehydrating agent for the preparation of isonitriles from formamides. This reagent 1 can readily be prepared, *in situ*, from thionyl chloride and *N,N*-dimethylformamide (DMF). Although isonitriles have been shown[14] to react with this reagent,



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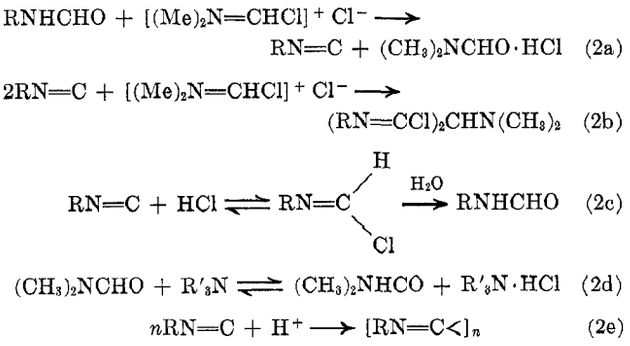
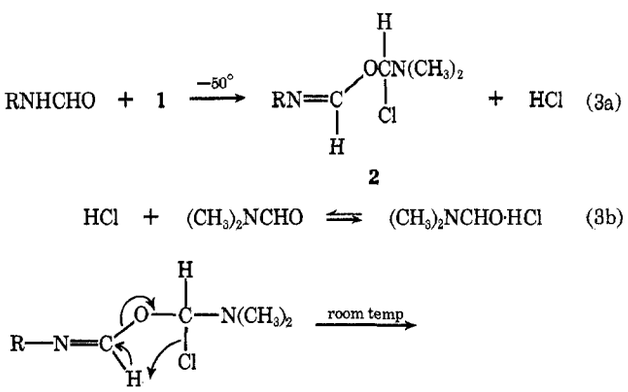
it was hoped that in the presence of a suitable base its dehydrative properties could be utilized.

Cyclohexylformamide was used as the model compound. When an equivalent of 1 in DMF was added to a DMF solution of cyclohexylformamide in the presence of triethylamine at 0°, the solution darkened. Although the characteristic isonitrile odor was evident, only a trace of isonitrile and starting formamide was isolated upon work-up of the reaction mixture. Higher temperatures did not improve the yield.

The low yield obtained was assumed to be due to the following factors. First, the isonitrile, once formed, could react with 1 as previously reported[14] (eq 2b). Second, although triethylamine reacts with hydrochloric acid, DMF likewise complexes with the acid so that, in an equilibrium situation, hydrochloric acid is kept in solution (eq 2b). Proton-catalyzed polymerization can result (eq 2e), or hydrochloric acid can add to the isonitrile which, after addition of water, gives back the starting formamide (eq 2c).



In order to circumvent reaction 2b, low temperatures (*ca.* −50°) were used. This was to allow the intermediate adduct 2 (eq 3) to form without decomposing



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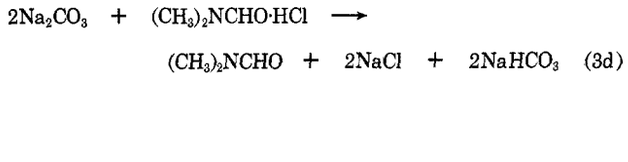

(1) The support of this work by grants from the National Science Foundation and Public Health Service Grant No. 04064 from the National Cancer Institute is gratefully acknowledged.

(2) For an excellent review of the various methods to prepare isonitriles, see I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offerman, *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965); I. Ugi, "Organic Chemistry," Vol. 20, Academic Press, New York, N. Y., 1971.

(3) H. L. Jackson and B. C. McKusick, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 438; J. Songstad, L. J. Strangeland, and T. Austad, *Acta Chem. Scand.*, **24**, 335 (1970).

(4) P. V. Fenzi and M. Arbasino, *Tetrahedron Lett.*, 4645 (1965); J. H. Boyer and J. Dejong, *J. Amer. Chem. Soc.*, **91**, 5929 (1969); T. Mukaiyama, and Y. Yokota, *Bull. Chem. Soc., Jap.*, **38**, 858 (1965).

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(6) J. C. Casanova, Jr., N. D. Werner, and R. E. Schuster, *J. Org. Chem.*, **31**, 3473 (1966); R. W. Horobin, N. R. Khan, J. McKenna, and B. G. Hutley, *Tetrahedron Lett.*, 5087 (1966); P. S. Matteson and R. A. Bailey, *J. Amer. Chem. Soc.*, **90**, 3761 (1969); K. Hartke, *Chem. Ber.*, **99**, 3163 (1966); H. Bredereck, B. Fohlisch, and K. Walts, *Justus Liebigs Ann. Chem.*, **686**, 92 (1965).

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(8) I. Ugi, R. Meyr, and M. Lipinski, *Org. Syn.*, **41**, 41 (1961).

(9) R. Wittman, *Angew. Chem.*, **73**, 219 (1961).

(10) R. Appel, R. Kleinstuck, and K.-D. Ziehn, *Angew. Chem., Int. Ed. Engl.*, **10**, 132 (1971).

(11) I. Ugi, W. Betz, U. Fetzer, and K. Offerman, *Chem. Ber.*, **94**, 2814 (1961); I. Ugi and F. Bodesheim, *ibid.*, **94**, 1157 (1961).

(12) O. Wallach and M. Hoffmann, *Justus Liebigs Ann. Chem.*, **184**, 75 (1877).

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 286, and references cited therein.

(14) Y. Ito, M. Okano, and R. Oda, *Tetrahedron*, **22**, 447 (1966).

immediately to the products (isonitrile and DMF) before the addition was completed. In this manner it was hoped that, after addition, the intermediate **2** could be decomposed at higher temperatures to give the desired isonitrile. To circumvent reactions 2c and 2d, solid sodium carbonate was added, after the addition of **1** to the formamide was completed, in order to irreversibly consume the hydrochloric acid and completely eliminate it from the reaction mixture. The result was that, as the reaction mixture warmed, it turned a pale yellow (*ca.* −15°) and then colorless (*ca.* 10°). Cyclohexylisonitrile was isolated in 87% yield after distillation.

Isonitrile formation with the Vilsmeier reagent appears to proceed as outlined in eq 3. In reaction 3a, the Vilsmeier reagent reacts at −50° with the formamide to produce intermediate **2** and hydrochloric acid, which immediately complexes with DMF (3b). After addition of sodium carbonate, the hydrochloric acid is irreversibly disposed of (3d) so that the elimination 2c can proceed, at ambient temperatures, in a slightly basic medium.

As can be seen from Table I, this procedure provides a general, convenient method for the preparation of isonitriles. Cyclic, acyclic, benzylic, cyclopropyl, vinylic, and aromatic isonitriles have been prepared in very good yields. Optically active isonitriles have also been prepared.

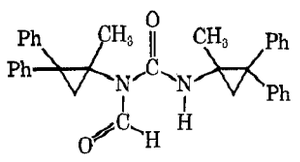
TABLE I

YIELDS OF VARIOUS ISONITRILES AS PREPARED BY THE $SOCl_2$–DMF REAGENT

RNC	Registry no.	Yield, %	Reaction scale, mol
Aliphatic			
n-Hexyl[a]		82	0.13
Cyclohexyl[b]		87	0.10
tert-Butyl[b]		55	0.20
1,1,3,3-Tetramethylbutyl[c]	14542-93-9	93	0.53
Benzylic			
Benzyl[b]		63	0.12
(*R*)-(+)-2-Phenyl-2-butyl	32528-86-2	92	0.04
1,1-Diphenylethyl	32528-87-3	90	0.08
Trityl[d]		95	0.27
		94	0.06
Cyclopropyl			
(*R*)-(−)-2,2-Diphenyl-1-methylcyclopropyl	32528-88-4	88	0.019
	32528-89-5[f]	70	0.003
Vinyl			
(*E*)-1,2-diphenylvinyl	32528-90-8	84	0.06
Aromatic			
Phenyl[b]		60	0.18
2,6-Dimethylphenyl[b]		74	0.11
p-Methoxyphenyl[e]		82	0.18
1-Naphthyl[b]		72	0.04

[a] M. Lipp, F. Dallacker, and I. M. Kocker, *Monatsh. Chem.*, **90**, 41 (1959). [b] See ref 3. [c] See ref 5. [d] N. E. Alexander, *J. Org. Chem.*, **30**, 1335 (1965). [e] I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960). [f] ± isomer.

The amides used in this work were usually obtained by the conventional formylation of the amine precursor using formic acid or *S*-ethyl thioformate. However, when the amine was not stable, *i.e.*, 1-amino-2,2-diphenyl-1-methylcyclopropane, or when the amine was not available as in the case of vinyl amines, then the amides were prepared by the reduction of isocyanates with lithium tri-*tert*-butoxylaluminum hydride. The reduction of isocyanates to formamides by lithium tri-*tert*-butoxylaluminum hydride was alluded to when it was reported[15] that 1 equiv of the hydride was consumed by phenyl isocyanate at 0°. However, isocyanates are known to dimerize and trimerize under mild basic conditions.[16] We have found that phenyl isocyanate with sodium borohydride in DMF results not in reduction but rather trimerization. Moreover, we have observed that the reduction of 1-methyl-2,2-diphenylcyclopropyl isocyanate with lithium tri-*tert*-butoxylaluminum hydride at ambient temperature did not produce the desired formamide but instead a compound (83% yield) whose physical data (see Experimental Section) were consistent with the structure **3**.



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When reduction was carried out at a low temperature (−15°), the desired formamide was obtained in 85% yield.

Experimental Section

Materials.—Industrial grade dimethylformamide (DMF) was purified by distilling a forecut at atmospheric pressure and then collecting the rest at 30–40 mm from barium oxide. Reagent grade tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Bulk solvents were distilled before use. All other reagent grade materials were used as received from the commercial supplier unless further purification was judged necessary.

1,1,3,3-Tetramethylbutylisonitrile (TMBI).—The following procedure was used to prepare all the isonitriles reported in Table I.

To a stirred solution of 83 g (0.528 mol) of *N*-(1,1,3,3-tetramethylbutyl)formamide[17] in 1 l. of DMF was added, under a nitrogen atmosphere, a solution of 40.3 ml (0.55 mol) of thionyl chloride dissolved in 150 ml of DMF at a rate so that the temperature never exceeded −50°. After addition, the bath was removed momentarily to allow the temperature to rise to −35°;[18] then it was replaced, and 118 g (1.11 mol) of anhydrous sodium carbonate was added. The bath was removed, and the reaction was stirred from 6 to 16 hr, during which time the temperature rose to 25°.[19] The mixture was diluted with ice-cold water in a separatory funnel and extracted into pentane. The extract was dried over sodium sulfate, evaporated, and distilled to yield 68.4 g (0.49 mol, 93%) of the isonitrile: bp 55.5–56.6° (11 mm) [lit.[5] bp 96–97° (69 mm)]; $n^{30}D$ 1.4178 (lit.[5] $n^{20}D$ 1.4214); d^{25} 0.7944; ir (neat) 2110 cm^{-1} (s); nmr (neat) δ 1.08 [s, 9, $C(CH_3)_3$], 1.43 [t, 6, J = 2 Hz, $C(CH_3)_2$], 1.58 (t, 2, J = 2.3 Hz, CH_2).

(*R*)-(+)-2-Amino-2-phenylbutane.[20]—To a solution of 6.8 g (0.0382 mol) of (*R*)-(−)-2-methyl-2-phenylbutanoic acid[21] [$[\alpha]^{24}_{5461}$ −33.6 ± 0.4° (*c* 2, benzene); mp 84–86°] in 90 ml of acetone and 6.1 ml (0.043 mol) of triethylamine was added 4.2

(15) H. C. Brown and P. M. Weisman, *Isr. J. Chem.*, **1**, 430 (1963).

(16) P. A. S. Smith, "The Organic Chemistry of Open-Chain Nitrogen Compounds," W. A. Benjamin, New York, N. Y., 1965.

(17) H. B. Henbest and M. J. W. Strattford, *J. Chem. Soc. C*, 995 (1966).

(18) For primary and secondary aliphatic and aromatic formamides, −45° is recommended.

(19) Alternatively, the reaction mixture was heated to 35° with rapid stirring and then stirring was continued at ambient temperature for 1 hr.

(20) D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.*, **85**, 1108 (1963).

(21) The acid was prepared and resolved according to the procedure of D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952).

ml (0.043 mol) of ethyl chloroformate dissolved in 10 ml of acetone at −10°.[22] After stirring for 2 hr, 4.2 g (0.065 mol) of NaN_3 in 45 ml of water was added dropwise. The mixture was stirred for an additional 4 hr, taken up in pentane, and extracted first with dilute hydrochloric acid and then with a sodium carbonate solution. After drying (sodium sulfate), the pentane was evaporated and the residue was placed in a vacuum desiccator for 4 hr. The crude azide was decomposed in refluxing benzene (5 hr) under a nitrogen atmosphere, the mixture was cooled to 0°, and 40 ml of concentrated hydrochloric acid was added dropwise. Stirring was continued at 10° for 48 hr, and the reaction mixture was then transferred to a separatory funnel, diluted with water, and extracted with ether. The aqueous layer was neutralized, and the amine was extracted into ether which was dried (sodium carbonate) and evaporated to give 4.8 g of material. Distillation yielded 4.1 g (0.0275 mol, 72%) of the optically pure amine: bp 58° (2.2 mm), 69° (3.7 mm) [lit.[20] bp 50–52° (2 mm)]; $[\alpha]^{24}_{5461}$ +18.1 ± 0.3° (*c* 3, benzene).

***N*-(1,1-Diphenylethyl)formamide.**—A solution of 30 g (0.152 mol) of 1-amino-1,1-diphenylethane[23] (prepared in 62% yield from 1,1-diphenylpropanoic acid[24] using the above procedure), 20 ml (0.35 mol) of 88% formic acid, and 150 ml of toluene was refluxed and the water was removed with the aid of a Dean–Stark apparatus. Evaporation to dryness and recrystallization of the residue from ethanol–water yielded 17.1 g (0.076 mol, 50%) of the formamide: mp 109.5–112°; ir (CCl_4) 3420 (w), 3382 (w), 3200 (broad), 1690 (s), 1596 (w), 1494 (w), 1447 (m), 693 cm^{-1} (s); nmr ($CDCl_3$) δ 1.97 and 2.13 (s, 3, CH_3, ratio 1.3:1.0), 6.7 and 7.4 (broad s, 1, NH, ratio 1:1.4), 7.12 and 7.16 (s, 10, aromatic, ratio 7.12 < 7.16), 7.75 and 7.94 (s, 1, CHO, ratio 1:1.4).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.95; H, 6.70; N, 6.33.

(*R*)-(+)-*N*-(1-Methyl-1-phenylpropyl)formamide.—To a refluxing solution of 7.10 g (0.0476 mol) of optically pure (*R*)-(+)-2-amino-2-phenylbutane in 50 ml of THF, in a flask equipped with a distilling column having an adjustable reflux control, was added a solution of 4.29 g (0.0476 mol) of *S*-ethyl thioformate in 25 ml of THF. Ethanethiol was removed as formed by regulating the reflux ratio. After the reflux temperature reached a constant level (65° for 4 hr), the excess THF was evaporated. The residual oil was taken up in methylene chloride, washed with diluted hydrochloric acid and sodium bicarbonate solution, and dried over magnesium sulfate. Removal of the solvent afforded 7.85 g (0.0443 mol, 93%) of analytically pure formamide: $[\alpha]^{24}_{5461}$ +9.37 ± 0.09° (*c* 4, dioxane); bp 82.5° (0.015 mm); ir (CCl_4) 3420 (w), 3390 (w), 3200 (m, broad), 2750 (w), 1688 (s), 692 cm^{-1} (s); nmr (CCl_4) δ 0.66 and 0.78 (t, 3, *J* = 7 Hz, CH_3, ratio 0.78 > 0.66), 1.55 and 1.57 (s, 3, CH_3, ratio 1.57 > 1.55), 1.8 (m, 2, CH_2), 7.03 and 7.17 (s, 5, aromatic, ratio 7.03 > 7.17), 7.33 and 8.12 (s, broad, 1, NH, ratio 2:1), 7.6–7.7 (m, 0.66, CHO), 7.87 (s, 0.33, CHO).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.78; H, 8.61; N, 7.95.

(±)-1-Carbazido-2,2-diphenyl-1-methylcyclopropane.—Following the above procedure, 19.8 g (0.0785 mol) of racemic 2,2-diphenyl-1-methylcyclopropanecarboxylic acid[25] together with 13.5 ml (0.097 mol) of triethylamine in 200 ml of acetone was treated with 8.7 ml (0.091 mol) of ethyl chloroformate in 30 ml of acetone and then with 9.8 g (0.15 mol) of sodium azide in 98 ml of water to yield 20.8 g of the crude azide. The azide was dissolved in 150 ml of pentane (25°), then cooled slowly to −78°. After decanting the pentane, the crystals were dried in a vacuum desiccator: yield 19.5 g (0.074 mol, 90%); mp 62–63° dec; ir (CCl_4) 2133, 1710, 1697, 1180, 1025 cm^{-1}; nmr (CCl_4) δ 1.15 (s, 3, CH_3), 1.45 (d, 1, *J* = 5 Hz, HCH), 2.30 (d, 1, *J* = 5 Hz, HCH), 7.1–7.6 (m, 10 aromatic).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.42; H, 5.41; N, 14.98.

(*R*)-(−)-1-Carbazido-2,2-diphenyl-1-methylcyclopropanecarboxylic Acid.—Similarly, 7.61 g (0.03 mol) of (*R*)-(+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid, $[\alpha]^{24}_{5461}$ +43.1° (*c* 2.3, $CHCl_3$), gave 7.83 (0.03 mol) of the crude azide, which was recrystallized from pentane to yield 7.36 g (0.0266 mol, 88%): mp 57–59° dec; $[\alpha]^{24}_{5461}$ −47.4 ± 0.2° (*c* 2, $CHCl_3$).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.81; H, 5.52; N, 15.11.

(*E*)-2,3-Diphenylpropenoyl Azide.—In a like manner, 24.1 g (0.107 mol) of (*E*)-2,3-diphenylpropenoic acid[26] gave a solution of the vinyl azide in acetone at −15°. The cold mixture was taken up in ether, diluted with water (0°), washed with ice-cold acid and base solutions, then dried over sodium sulfate at −10°. Evaporation (0°) of the solvent followed by low-temperature vacuum drying gave 24.8 g of the crude azide, mp 62–65° dec. Recrystallization was accomplished from a 50:50 methylene chloride–pentane mixture by dissolving the azide at 10–15° in a minimum amount of solvent followed by cooling in a Dry Ice–acetone bath to yield 23.2 g (0.093 mol, 87%) of the pure azide:[27] mp 68–70° dec; ir (CCl_4) 3060, 2130 (s), 1692 and 1683 (s), 1616 (m), 1372 (m), 685 cm^{-1} (s); nmr ($CDCl_3$) δ 6.8–7.6 (m, 10, aromatic), 7.87 (s, 1, vinyl).

(±)-*N*-(2,2-Diphenyl-1-methylcyclopropyl)formamide.—A solution of 18.5 g (0.067 mol) of racemic 1-carbazido-2,2-diphenyl-1-methylcyclopropane in benzene was refluxed for 6 hr to yield 16.6 g (0.066 mol) of the isocyanate (a thick oil), ir (CCl_4) 6124, 4500, 2265 cm^{-1}. The isocyanate was transferred to an addition funnel with 100 ml of anhydrous THF and added slowly (3 hr) to a solution of 25 g (0.1 mol) of lithium tri-*tert*-butoxyaluminum hydride in 150 ml of THF at −15°. After 2 hr of additional stirring, 50 ml of 50% formic acid was added dropwise with fast mechanical stirring (−15°). The mixture was taken up in ether, washed with dilute hydrochloric acid and saturated sodium carbonate solution, and dried over magnesium sulfate. Evaporation of the solvent gave 17 g of the crude formamide, which was crystallized from chloroform–hexane to yield 14.2 g (0.57 mol, 85%), mp 114–114.5°. Recrystallization gave the pure formamide: mp 115.5–116.5°; ir (CCl_4) 3415 (w, doublet), 2750 (w), 1704 (s), 1215 cm^{-1} (s); nmr δ 1.41 (s, 3, CH_3), 1.3–1.9 (m, 2, CH_2), 5.95 (s, broad, 1, NH), 7.1–7.7 (m, 10, aromatic), 7.82 (1, CHO).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.97; N, 5.55.

(*R*)-(−)-*N*-(2,2-Diphenyl-1-methylcyclopropyl)formamide.—Similarly, 4.14 g (0.015 mol) of optically pure (*R*)-(−)-1-carbazido-2,2-diphenyl-1-methylcyclopropane yielded 3.1 g (0.012 mol) of the formamide, mp 138–140°, $[\alpha]^{24}_{5461}$ −99.1 ± 0.5° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.86; N, 5.56.

(*E*)-*N*-(1,2-Diphenylvinyl)formamide.—In like manner, 19.2 g (0.077 mol) of (*E*)-2,3-diphenylpropenoyl azide was refluxed in 150 ml of hexane for 4 hr to give the isocyanate: ir (neat) 3055, 2255 (s), 1635 (m), 1359 (m), 989, 691 cm^{-1} (s). Reduction with lithium tri-*tert*-butoxyaluminum hydride yielded 16.9 g (0.0757 mol, 98%), mp 106–108°. Recrystallization from chloroform–petroleum ether (bp 30–60°) gave 16.2 g (0.0727 mol, 94%): mp 109–110°; ir (CCl_4) 3420 and 3390 (w), 3195 (w, broad), 2965 (w), 2870 (w, broad), 1704 and 1693 (s), 1635 (m), 1371 (m), 688 cm^{-1} (m); nmr ($CDCl_3$) δ 6.32 (s, 1, vinyl), 6.7–7.5 (m, 10, aromatic), 8.1–8.6 (m, 2, –NHCHO).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.64; H, 5.95; N, 6.30.

Reduction of (*R*)-2,2-Diphenyl-1-methylcyclopropyl Isocyanate at 25°.—In a similar manner, the (*R*)-cyclopropyl isocyanate [prepared from 7.11 g (0.0256 mol) of the (*R*)-(−)-cyclopropyl azide] was added to a THF solution of 9.8 g (0.038 mol) of lithium tri-*tert*-butoxyaluminum hydride at 25°. Crystallization of the product afforded 5.29 g (0.021 mol, 83%) of a compound whose physical data were consistent with **3**: mp 177.5–179.5°; $[\alpha]^{24}_{5461}$ −267 ± 2° (*c* 1, $CHCl_3$); ir (CCl_4) 3278 (m), 1716 (s), 1681 (m), 1515 cm^{-1} (m); nmr ($CDCl_3$) δ 1.2–2.2 (m, 10), 6.3–8.6 (m, 22); mass spectrum (70 eV) *m/e* 500 (P), 472 (P − CO).

Anal. Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44; N, 5.48. Found: C, 81.67; H, 6.43; N, 5.57.

1,1-Diphenyl-1-ethylisonitrile.—Following the general procedure, 18.1 g (0.080 mol) of *N*-(1,1-diphenylethyl)formamide in 300 ml of DMF was treated with 5.2 ml (0.084 mol) of thionyl chloride in 15 ml of DMF and 18 g (0.17 mol) of sodium carbonate to give after distillation 15.0 g (0.73 mol, 90%) of the isonitrile: bp 74–75° (0.025 mm); ir (neat) 2120 (s), 1598 (m), 1493 (s),

(22) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(23) I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1965.

(24) P. L. Pickard and E. F. Engles, *J. Amer. Chem. Soc.*, **73**, 864 (1951).

(25) H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *ibid.*, **83**, 2517 (1961).

(26) R. E. Buckles and K. Bremer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 777.

(27) The azide decomposes slowly at room temperature to the isocyanate.

1447 (s), 690 cm^{-1} (s); nmr (CCl_4) δ 1.97 (s, 3, CH_3), 6.9–7.35 (m, 10, aromatic).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 87.02; H, 6.44; N, 6.56.

(*R*)-(+)-2-Phenyl-2-butylisonitrile.—Following the general procedure, 7.85 g (0.044 mol) of (*R*)-(+)-*N*-(1-methyl-1-phenylpropyl)formamide in 150 ml of DMF yielded, after distillation, 6.51 g (0.041 mol, 92%) of the optically pure isonitrile: bp 96.97° (9 mm); $[\alpha]^{24}_{5461}$ +2.87 ± 0.07° (*c* 3, dioxane); ir (neat) 2125 (s), 1498 (m), 755 (s), 692 cm^{-1} (s); nmr (CCl_4) δ 0.84 (t, 3, J = 7 Hz, CH_3), 1.67 (t, 3, J = 2 Hz, CH_3), 1.90 (m, 2, J_{AB} = 7 Hz, J_{AC} = 2 Hz, CH_2), 7.40 (m, 5, aromatic).

Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 83.08; H, 8.45.

(*E*)-1,2-Diphenylvinylisonitrile.—Similarly, 14.2 g (0.0637 mol) of (*E*)-*N*-(1,2-diphenylvinyl)formamide in 400 ml of DMF was treated with the DMF–$SOCl_2$ reagent, however, at −60°. The mixture was allowed to stir at −50° for 10 min prior to the addition of sodium carbonate. The mixture was taken up in 50:50 ether–pentane for the washings, and the organic layer was dried over sodium sulfate. Evaporation of the solvent gave 10.9 g (0.0532 mol, 84%) of the isonitrile, bp 109° dec (0.03 mm), which contained only a trace of the formamide. Prior to use small quantities were purified by molecular distillation at high vacuum to prevent decomposition (the isonitrile darkens on standing): ir (neat) 2105 (s), 1620 (w), 1372 (m), 689 cm^{-1}; nmr ($CDCl_3$) δ 6.94 (s, vinyl), 6.9–7.5 (m, aromatic). Mass spectral data are shown in Table II.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.83. Found: C, 87.46; H, 5.44; N, 6.68.

(±)-2,2-Diphenyl-1-methylcyclopropylisonitrile.—In a like manner, 4.68 g (0.0187 mol) of racemic *N*-(2,2-diphenyl-1-methylcyclopropyl)formamide in 93 ml of DMF was treated with the thionyl chloride–DMF reagent. After the mixture had stirred for 16 hr, the contents of the flask were rinsed into a beaker with THF; 400 ml of cold water was added slowly at 0°. The precipitate was collected, washed with water, and dried to yield 4.35 g of material, mp 109–115°. Crystallization from chloroform–petroleum ether gave 3.84 g (0.017 mol, 88%) of the isonitrile: mp 118–129°; ir (CCl_4) 2120 (s), 1494 (s), 684 cm^{-1} (s); nmr ($CDCl_3$) δ 1.38 (s, 3, CH_3), 1.56 (d, 1, J_{AB} = 6 Hz, HCH), 1.93 (d, 1, J_{AB} = 6 Hz, HCH), 7.1–7.9 (m, 10, aromatic).

TABLE II

Peak	Obsd mass	Calcd mass	Anal.	Rel intensity
P + 1	206.0913	206.0924	$C^{13}C_{14}H_{11}N$	19.7
P	205.0884	205.0890	$C_{15}H_{11}N$	100.0
P − H	204.0788	204.0812	$C_{15}H_{10}N$	92.4
P − HCN	178.0745	178.0782	$C_{14}H_{10}$	32.4
P − C_7H_5N	102.0430	102.0469	C_8H_6	24.5
P − C_8H_6N	89.0378	89.0391	C_7H_5	23.6

Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.47; H, 6.58; N, 5.94.

(*R*)-(−)-2,2-Diphenyl-1-methylcyclopropylisonitrile.—Similarly, 0.8354 g (0.00329 mol) of optically pure (*R*)-(−)-*N*-(2,2-diphenyl-1-methylcyclopropyl)formamide in 25 ml of DMF was treated with 0.28 ml (0.038 mol) of thionyl chloride in 1.5 ml of DMF followed by 0.81 g (0.0076 mol) of sodium carbonate. The precipitate, 0.726 g, mp 140–149°, was crystallized from benzene–petroleum ether: yield 0.537 g (0.00231 mol, 70%); mp 150.5–152°; $[\alpha]^{25}_{5461}$ −166 ±1° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.47; H, 6.58; N, 5.94.

Registry No.—**3**, 32529-00-3; (*R*)-(+)-2-amino-2-phenylbutane, 10181-67-6; *N*-(1,1-diphenylethyl)-formamide, 32528-92-0; (*R*)-(+)-*N*-(1-methyl-1-phenylpropyl)formamide, 32528-93-1; (±)-1-carbazido-2,2-diphenyl-1-methylcyclopropanol, 32528-94-2; (*R*)-(−) isomer, 32528-96-4; (*E*)-2,3-diphenylpropenoyl azide, 32528-95-3; (±)-*N*-(2,2-diphenyl-1-methylcyclopropyl)formamide, 32528-97-5; (*R*)-(−) isomer, 32528-98-6; (*E*)-*N*-(1,2-diphenylvinyl)formamide, 32528-99-7.

The Base-Catalyzed Dehydrohalogenation of Two Isomeric 3,4-Dibromo-2-ethoxytetrahydropyrans[1]

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The reactions of the two isomers, 3α,4β-dibromo-2α-ethoxytetrahydropyran (**1a**) and 3α,4β-dibromo-2β-ethoxytetrahydropyran (**1b**), with refluxing ethanolic sodium ethoxide have been examined. Total yields of isolable products were 19–38%. Compound **1a** afforded *trans*-5,6-diethoxy-5,6-dihydro-2*H*-pyran (**6**), *cis*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (**7c**), and *trans*-2,5-diethoxy-5,6-dihydro-2*H*-pyran (**7t**) in the relative proportion 5.6:4.8:1.6, along with a trace of 3-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (**2**). Compound **1b** furnished the same products **6**, **7c**, **7t**, and **2** in the relative proportion 1:1:16:6. The diethoxydihydropyrans were stable under the reaction conditions, but compound **2** reacted further to produce **6**, **7c**, and **7t** in the proportion 1.4:3.5:22.9.

It has been reported[4] that the reaction of hot ethanolic potassium hydroxide or sodium ethoxide with a mixture of the two isomers of 3,4-dibromo-2-ethoxytetrahydropyran **1a** and **1b** produces in poor yield a mixture containing 3-bromo-2-ethoxy-5,6-dihydro-2*H*-pyran (**2**) and a compound suggested to be 2,4-diethoxy-5,6-dihydro-2*H*-pyran (**3**) (Scheme I). Prolonged treatment of the mixture of dibromides **1a** and **1b** under these conditions led to a bromine-free product from which was isolated by distillation a diethoxydihydropyran **3**. Compound **2** was isolated in 50% yield by dropping a solution of **1a** and **1b** in toluene onto molten potassium hydroxide. Neither of the structures **2** or **3** was definitely established. Compound **2** was assigned its structure on the basis of the analogy to the behavior of α,β-dibromocarbonyl compounds in dehydrobromination reactions. A tentative assignment of the structure of **3** was based on the finding that catalytic hydrogenation of **3** gave a diethoxytetrahydropyran **5** (evidence for one double bond in **3**) and that acid hydrolysis of **3**, followed by phenylhydrazone formation from the hydrolysis product, gave a substance which contained one ethoxy group.

(1) Partly from the thesis of Sweet, submitted in 1968 to the Faculty of Graduate Studies, University of Alberta, as part of the requirements for the Ph.D. degree.

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(4) G. F. Woods and S. C. Temin, *J. Amer. Chem. Soc.*, **72**, 139 (1950).