Anal. Calcd for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.66; H, 6.53; N, 4.71.

A sample of (−) **8**, $[\alpha]^{30}$ −21.73° (*c* 8.0) (96% optically pure), was converted into the methyl ether, (+) **9**, as follows. (−) **8**, 200 mg (1.43 mmol), was converted into the potassium salt in 10 ml of tetrahydrofuran as described above for preparation of the acid phthalate derivative. To the stirred solution at room temperature under nitrogen was added 170 mg (1.20 mmol) of methyl iodide in 5 ml of tertrahydrofuran. The mixture was stirred at room temperature for 1 hr, 1 ml of water was added, and the solution was concentrated under reduced pressure. The residue was shaken with a mixture of 15 ml of pentane and 15 ml of water. The organic layer was separated, dried ($MgSO_4$), and the pentane removed with a fractionation column. The residue was purified by preparative gc (20-ft column, 30% Carbowax 20M on Chromosorb at 150°). The yield was 122 mg (55%) and (+) **9** was >99.4% pure (glpc) and had $[\alpha]^{30}D$ 33.27° (*c* 10.0). Presumably this material is 96% optically pure.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.99; H, 11.75.

Registry No.—(−) **1**, 18366-92-2; (+) **2**, 16651-55-1; (+) **4**, 18366-94-4; (−) **5**, 18366-95-5; (+) **6**, 18366-96-6; (+) **7**, 18366-97-7; (−) **8**, 18366-98-8; (+) **9**, 18366-99-9.

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Nitrilium Salts. A New Method for the Synthesis of Secondary Amines[1]

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A new method for the synthesis of secondary amines is described involving the sodium borohydride reduction of imino esters prepared from nitrilium salts. This conversion of nitriles into secondary amines proceeds in high yield and has been applied to a variety of compounds. The nitrilium salts are easily prepared from nitriles and dialkoxycarbonium fluoroborates (**5**), which are readily available from the corresponding ortho esters. Although most of the compounds examined gave the corresponding secondary amines as exclusive products, alkylation with di-*n*-propoxycarbonium fluoroborate (**5c**) gave the rearranged isopropylamine as the major product. The mechanism of the over-all reaction is discussed in light of intermediates observed, and a mechanism for the rearrangement is suggested.

Although nitrilium salts have been known for some time, little is known about the chemistry of these compounds. N-Ethylnitrilium salts (**2**) have been synthesized by reaction of nitriles with triethyloxonium fluoroborate[2] and with diethoxycarbonium hexachloroantimonate.[3] The powerful electrophilicity of these salts has been demonstrated[2] by their instantaneous conversion to amides upon treatment with water. Although there are numerous methods available for the synthesis of amines,[4] the conversion of a nitrile into a secondary amine requires vigorous reducing conditions which preclude selective reduction with other easily reduced functional groups present. Our need for such a selective method for the conversion of a nitrile into a secondary amine for a total synthesis currently under investigation prompted us to examine the reduction of these nitrilium salts.

Initial efforts were directed toward the synthesis of N-ethylnitrilium salts based on Meerwein's procedure[2] and the subsequent reduction of these salts by metal hydrides. The nitrilium salts (**2**) were readily prepared by refluxing the nitrile and 2 equiv of triethyloxonium fluoroborate in methylene chloride; reaction of **2** with absolute ethanol, followed by treatment with sodium borohydride in methanol at 0° or in ethanol at 25°, afforded good yields of the corresponding secondary amine (**4**) (Scheme I). The nitrilium salt is rapidly converted into imino ester **3** which undergoes slow reduction to the secondary amine. The reaction proceeds well for aromatic nitriles and for primary-, secondary-, and tertiary-substituted aliphatic nitriles.[1a]

SCHEME I

$$\underset{\mathbf{1}}{RC{\equiv}N} + Et_3O^+BF_4^- \text{ or } \mathbf{5b} \xrightarrow[\text{reflux}]{CH_2Cl_2} \underset{\mathbf{2}}{RC{\equiv}\overset{+}{N}CH_2CH_3\,BF_4^-} \xrightarrow[\text{fast}]{EtOH} \underset{\mathbf{3}}{RC(OEt){=}NCH_2CH_3} \xrightarrow[\text{slow}]{NaBH_4} \underset{\mathbf{4}}{RCH_2NHCH_2CH_3}$$

R = −Ph, −CH_2Ph, −$CHPh_2$, −$(CH_2)_3CH_3$, −$CH(CH_3)_2$, −$C(CH_3)_3$

Attention was then directed to the synthesis of nitrilium salts other than the N-ethyl compounds. Because of the difficulties which Meerwein encountered in the preparation of trialkyloxonium fluoroborates containing groups larger than ethyl,[5] we turned to a modification of Meerwein's method[6] for the preparation of diethoxycarbonium fluoroborate (**5b**) in the hope that other dialkoxycarbonium fluoroborates could be made from other ortho esters. Thus **5b** was prepared by reaction of triethyl orthoformate with boron trifluoride etherate at −30° in methylene chloride; this compound proved to be an efficient ethylating agent for nitriles and afforded yields of secondary amines comparable with those obtained with triethyloxonium fluoroborate.

Our hope that the alkylating species could be varied

(1) (a) A preliminary report of this work has appeared: R. F. Borch, *Chem. Commun.*, 442 (1968). (b) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31–April 5, 1968.

(2) H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1965).

(3) S. Kabuss, *Angew. Chem. Intern. Ed. Engl.*, **5**, 675 (1966).

(4) For a general reference, see Houben Weyl's "Methoden der organischen Chemie," Vol. XI, Part I, G. Thieme Verlag, Stuttgart, 1957.

(5) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

(6) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Ann.*, **632**, 38 (1960).

by utilizing different ortho esters was fully justified. The reaction of boron trifluoride etherate with ortho esters is in fact a general reaction, and by judicious choice of solvent the dialkoxycarbonium fluoroborates (**5**) can be isolated as crystalline products at low temperatures. The detailed structural analysis of these compounds has been reported elsewhere.[7] All of these dialkoxycarbonium fluoroborates can be used successfully in the conversion of nitriles into the corresponding amines **8**; the results are summarized in Table I.

TABLE I

SUBSTITUTED BENZYLAMINES FROM BENZONITRILE AND DIALKOXYCARBONIUM FLUOROBORATES IN METHYLENE CHLORIDE

Reagent	Ratio of reagent:nitrile	Time, hr	Temp, °C	Yield, % Nitrilium salt **6**	Yield, % Imino ester **7**	Amine **8**	Yield, % Anal.[a]	Yield, % Isolated
5a[c]	2:1	18	25	18	74	$PhCH_2NHCH_3$	79	73[b]
5b	2:1	15	40	52	35	$PhCH_2NHCH_2CH_3$	71	68[b]
5b	1:1	210	25	41	42	$PhCH_2NHCH_2CH_3$	70	66
5c	3:1	18	25	14	20	$PhCH_2NHCH_2CH_2CH_3$	28	
				27	33	$PhCH_2NHCH(CH_3)_2$	53	
5d	1.5:1	1	25	99	0	$PhCH_2NHCH(CH_3)_2$	94	89[b]
5e	2:1	3	25	0	83	$PhCH_2NHCH_2CH{=}CH_2$	80	72

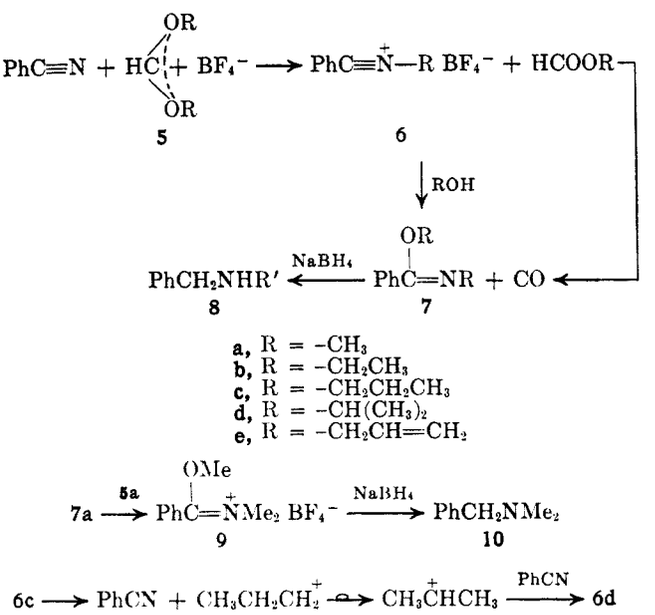
[a] Determined by gas chromatographic analysis. [b] Isolated as the hydrochloride. [c] Reaction run in 3:1 CH_2Cl_2–CH_3NO_2.

Although the reaction of nitriles with triethyloxonium fluoroborate leads to the nitrilium salt as the exclusive product, reaction under similar conditions with the dialkoxycarbonium fluoroborates (**5**) leads to significant amounts of imino ester **7** in addition to the nitrilium salt (**6**) (*cf.* Table I). We tentatively explain the imino ester formation by assuming that the alkyl formate, a by-product of the reaction, is acting as an alkoxy group donor in the strongly polar medium and is slowly decomposing to give the protonated imino ester (**7** HBF_4) and CO. This theory is supported by the fact that, if benzonitrile is alkylated with triethyloxonium fluoroborate in the presence of 1.2 equiv of *n*-propyl formate, 80% of the N-alkylated material is present as the O-propyl imino ester. In the absence of *n*-propyl formate, the nitrilium salt is the exclusive product.

Diisoproxy- and diallyloxycarbonium fluoroborates (**5d** and **5e**) are much less stable than the reagents derived from primary alkyl groups, presumably because of more facile dissociation to carbonium ions. Their reaction with nitriles is correspondingly faster, being complete in 1–3 hr at 25°; prolonging the reaction time diminishes the yields by conversion of nitrilium salt into N-isopropylamide in the former case and by polymerization of the nitrilium salt in the allyl case. To obtain satisfactory yields with dimethoxycarbonium fluoroborate, it is necessary to isolate the imino ester **7a** by hydrolytic work-up before reduction. If the reaction mixture is reduced directly, significant amounts (up to 35%) of dimethylated amine (**10**) are obtained (Scheme II). This unusual by-product might arise from further alkylation of imino ester **7a** to give iminium salt **9**; the conversion of these salts into tertiary amines by borohydride reduction is known.[8]

Although di-*n*-propoxycarbonium fluoroborate (**5c**) is a stable species,[7] the nitrile alkylation product is a mixture of *n*-propylamine and isopropylamine (*cf.* Table I). The rearrangement must be occurring in the nitrilium salt prior to imino ester formation, inasmuch as pure *n*-propylamine **8c** was obtained upon reduction of pure *n*-propyl imino ester **7c**. There are two plausible mechanisms for this rearrangement: (a) rearrangement is taking place in the alkylation step, or (b) alkylation proceeds normally to the *n*-propylnitrilium salt, and the salt subsequently rearranges by dissociation–recombination. The ratio

SCHEME II



of isopropyl–*n*-propyl in the product varies with time in the early stages of the reaction (see Experimental Section); only after 8 hr (60% completion) does the ratio become invariant. If the rearrangement were occurring in the alkylation step one would expect the product ratio to be constant throughout the reaction. Therefore we favor the dissociation–recombination mechanism.

We are presently unable to explain the significance of the product ratio, however. The product specificity in the isopropyl case precludes a free equilibrium between the nitrilium salts; moreover, this ratio is markedly temperature dependent, changing to 69:31 in favor of the *n*-propyl compound at −15°. Presumably the product ratios are controlled by the rate of rearrangement of nitrilium salt coupled with the rate of quenching to imino ester.

(7) R. F. Borch, *J. Amer. Chem. Soc.*, **90**, 5303 (1968).
(8) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

Experimental Section[9]

Preparation of Dialkoxycarbonium Fluoroborates (5). Diethoxycarbonium Fluoroborate (5b).—To 16.5 ml (0.1 mol) of triethyl orthoformate at −30° was added a solution of 15 ml (0.12 mol) of boron trifluoride etherate in 12 ml of methylene chloride dropwise with stirring over 15 min. When the addition was completed, the mixture was warmed to 0° and stirred 10 min. Anhydrous ether (15 ml) was added, and the mixture was cooled to −70°. The supernatant was removed by filtration through a filter stick. The solid residue was washed with 20 ml of 1:1 methylene chloride–ether at −70°, and the supernatant was again removed by filtration. Traces of solvent were removed *in vacuo* to give a hygroscopic solid which melted between 0 and 10°, yield 14.7 g (86%). The structure was confirmed by nmr analysis.[7]

Di-*n*-propoxycarbonium fluoroborate (5c) was prepared in 82% yield exactly as described for **5b** from tri-*n*-propyl orthoformate[10] and BF_3 etherate.

Diisopropoxycarbonium fluoroborate (5d) was pepared in 68% yield exactly as described for **5b** from triisopropyl orthoformate[10] and BF_3 etherate.

Dimethoxycarbonium Fluoroborate (5a).—To 5.5 ml (50 mmol) of trimethyl orthoformate at −30° was added a solution of 7.3 ml (56 mmol) of BF_3 etherate in 6 ml of methylene chloride dropwise with stirring over 5 min. The mixture was brought to 0°, stirred 15 min, cooled to −30°, and filtered. The solid product was suspended in 5 ml of methylene chloride at −70°, the lumps were broken up with a glass rod, and the solid was filtered. Traces of solvent were removed *in vacuo* to give 5.74 g (85%) of solid which melted near 20°.

Diallyloxycarbonium Fluoroborate (5e).—To 2.38 g (13 mmol) of triallyl orthoformate[10] was added a solution of 2.0 ml (15 mmol) of BF_3 etherate in 2 ml of methylene chloride at −70° with stirring over 5 min. The solution was brought to 0°, stirred 5 min, and 5 ml of anhydrous ether was added. The product separated out as an oil upon cooling to −70°, and the upper layer was removed by decantation and discarded. The viscous oil remaining was dissolved in 2 ml of methylene chloride, cooled to −70°, and 5 ml of anhydrous ether was added. The upper layer was again separated by decantation, and the oily product was freed of traces of solvent *in vacuo* below 0°. This material was used without further purification, yield 1.75 g (73%).

Preparation of N-Substituted Ethylamines.—The procedure for ethyl-*n*-amylamine is typical. A solution of 0.94 ml (9 mmol) of valeronitrile and 3.45 g (18 mmol) of triethyloxonium fluoroborate[11] in 5 ml of methylene chloride was refluxed with stirring under nitrogen for 48 hr. [If diethoxycarbonium fluoroborate (18 mmol) is used, reflux time should be reduced to 19 hr.] An aliquot was removed and quenched with water; glpc analysis on the organic phase showed 6% valeronitrile, 1% imino ester **3** (R = *n*-C_4H_9), and 93% N-ethylvaleramide. The reaction mixture was cooled to 0°, and 1 ml of absolute ethanol was added. The methylene chloride was removed *in vacuo*, and the residue was dissolved in 25 ml of methanol. To this solution at 0° was cautiously added with stirring 2 g of sodium borohydride in portions (vigorous gas evolution). After stirring 1 hr at 0° the solution was brought to pH 1 with 6 *N* HCl, and the methanol was removed *in vacuo*.[12] The residue was dissolved in 20 ml of water, brought to pH 10 with 6 *N* NaOH, saturated with sodium chloride, and extracted with four 10-ml portions of ether. The combined extracts were dried ($MgSO_4$) and the ether was removed by distillation through a 15-cm Vigreux column.[12] The residue (1.23 g) on glpc analysis showed 70% ethyl-*n*-amylamine[13] and 30% methanol, analytical yield 860 mg (83%).

The crude product was dissolved in 25 ml of anhydrous ether, and gaseous HCl was passed through the solution. The hydrochloride crystallized from the solution and had mp 196–197° (lit.[14] mp 195°), yield 1.04 g (76%).

Preparation of N-Substituted Benzylamines.—The procedure for N-isopropylbenzylamine (**8d**) is typical, except for reaction times (see Table I). A solution of 0.74 ml (7.3 mmol) of benzonitrile and 2.40 g (11.4 mmol) of **5d** in 3 ml of methylene chloride was stirred at room temperature for 1 hr. An aliquot was removed and quenched with water; glpc on the organic phase showed 1% benzonitrile–99% isopropylbenzamide. The solution was cooled to 0°, and 1 ml of absolute ethanol was added. The resulting mixture was poured into 10 ml of ice-cold 3 *N* NaOH and extracted with four 10-ml portions of ether. The combined extracts were dried ($MgSO_4$); the solvent was removed *in vacuo*. The crude imino ester was dissolved in 15 ml of ethanol containing 1 g of sodium borohydride, and the resulting solution was stirred 18 hr at 25°. Most of the ethanol was removed at reduced pressure, and the residue was suspended in 10 ml of water and extracted with four 10-ml portions of ether. The combined extracts were dried ($MgSO_4$); the solvent was removed *in vacuo* to give 1.06 g of crude product. Glpc analysis showed it to be 95% pure N-isopropylbenzylamine (**8d**), analytical yield 1.00 g (94%).

The hydrochloride was prepared as above, yield 1.21 g (89%), mp 192–194° (lit.[15] mp 195°).

Reaction of Benzonitrile with 5c. Analysis of Product Ratios.—A solution of 0.15 ml of benzonitrile, 785 mg of **5c**, and 1 cc of methylene chloride was stirred at 25° for 24 hr. At intervals a 25-μl aliquot was removed and added to 0.1 ml of 1-propanol. Two drops of 6 *N* NaOH was added, followed by 2 ml of water. The organic layer was analyzed directly on glpc; the results are summarized in Table II.

TABLE II

PRODUCT ANALYSIS FROM THE REACTION OF BENZONITRILE WITH DI-*n*-PROPOXYCARBONIUM FLUOROBORATE

Time, hr	Unreacted nitrile, %	PhC(OPr)=N-*n*-pr,[a] %	PhC(OPr)=N-*i*-pr,[a] %	Ratio of *i*-pr:*n*-pr
2	81	8.8	10.2	46:54
3	67.5	15.5	17.0	48:52
4	58	22.8	19.2	54:46
7	44	33	23	58:42
8	40	38	22	64:36
11	22	50	28	64:36
24	5	62	33	65:35

Registry no.: [a] 18354-87-5. [b] 18354-88-6.

Registry No.—**5a**, 18346-68-4; **5b**, 1478-41-7; **5c**, 18346-70-8; **5d**, 18346-71-9; **5e**, 18346-72-0; **8a** HCl, 13426-94-3; **8b** HCl, 5417-36-7; **8b**, 14321-27-8; **8d** HCl, 18354-85-3; **8e**, 4383-22-6; benzonitrile, 100-47-0; methylene chloride, 75-09-2.

Acknowledgment.—The author is grateful to The Petroleum Research Fund (No. 710-G), administered by the American Chemical Society, and to the Graduate School of the University of Minnesota for generous financial support.

(9) Gas chromatographic analyses were run on a Varian Aerograph Model 90-P3 chromatograph. using a 0.25 in. × 10 ft column packed with 15% FFAP on Chromosorb W. Melting points were taken on a hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer.

(10) The ortho esters were prepared by acid-catalyzed exchange between trimethyl orthoformate and the appropriate alcohol with continuous removal of the methanol formed; see R. M. Roberts, T. D. Higgins, Jr., and P. R. Noyes, *J. Amer. Chem. Soc.*, **77**, 3801 (1955).

(11) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(12) For less volatile amines (a) it is not necessary to acidify the reaction mixture before removing the methanol *in vacuo* and (b) the final removal of solvent can be effected more efficiently *in vacuo*.

(13) The identity of the products was confirmed throughout by comparison of ir and nmr spectra and glpc retention times with those of authentic samples prepared by the $LiAlH_4$ reduction of the corresponding N-alkylamides.

(14) E. J. Schwoegler and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 3499 (1939).

(15) R. E. Lutz, P. S. Bailey, R. J. Rowellett, Jr., J. W. Wilson III, R. K. Allison, M. T. Clark, N. H. Leake, R. H. Jordan, R. J. Keller, III, and K. C. Nicodemus, *J. Org. Chem.*, **12**, 760 (1947).