Table II
Reaction of Aromatic Compounds with Potassium Thiocyanate in HF

Substrate (g)	KSCN, g, mol	Temp, °C	Conversion,[a] %	Product (g)	Registry no.
Toluene (6.4)	4.9, 0.050	25	36	*p*-Methylthiobenzamide[b] (2.7)	2362-62-1
Anisole (7.6)	4.9, 0.050	25	61	*p*-Methoxythiobenzamide[c] (5.1)	2362-64-3
Benzene (5.5)	4.9, 0.050	25			

[a] Based on potassium thiocyanate. [b] Recrystallized from benzene–petroleum ether, mp 169–171° (lit.[9] mp 172°). [c] Recrystallized from benzene, mp 145–147° (lit.[10] mp 148.5–149.5°).

mation of 1 from KXCN and HF. These species might well have different selectivities. The striking difference in isomer distribution obtained in the reaction with toluene at 25 and 100° might be due to a change in the relative proportion of reactive species with temperature.

Several aspects of the data in Tables I and II deserve further comment. The isomer ratios and relative conversions obtained in the amidation reactions are, in general, normal for electrophilic aromatic substitution reactions.[1] In particular, the exclusive formation of *p*-fluorobenzamide from fluorobenzene is in line with previous observations[6] for this compound. The failure of aniline and pyridine to react is reasonable as their protonation in HF would result in strong deactivation toward electrophilic attack. The exclusive formation of the para isomers with the thiocyanate reagent may reflect a less reactive, more selective nature of this species relative to KOCN, although the greater size of the sulfur reagent relative to the oxygen reagent could account for the exclusive formation of the para isomers.

Experimental Section

General. Potassium cyanate and potassium thiocyanate (Fisher) were dried in a vacuum oven at 105°. Anhydrous hydrogen fluoride was obtained in a cylinder from Air Products and used as received. The aromatic substrates were reagent grade and used without purification. GLC analyses were performed on a Hewlett-Packard 5700 instrument with thermal conductivity detector using the indicated column and conditions. Peak areas are not corrected for relative detector response. Melting points were measured on a Thomas-Hoover melting point apparatus and are corrected.

Caution. Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow-healing burns. Laboratory work with HF should be conducted only in an efficient hood with operator wearing full face shield and protective clothing.[11]

Procedure. Reactions at room temperature were run in a 170-ml Kel-F vessel. Higher temperature reactions were run in an 80-ml Hastelloy pressure bomb. Potassium cyanate or thiocyanate (0.03–0.05 mol) and excess aromatic were introduced into the reaction vessel. The vessel was cooled in dry ice–acetone or liquid N_2, evacuated, and charged with 40 g of liquid HF. The vessel was closed, warmed to the reaction temperature, and shaken (Hastelloy bomb) or stirred (Kel-F vessel) for 4 hr. The HF and excess aromatic were removed by aspirator vacuum. The residue was partitioned between water and ether. The ether solution was dried ($MgSO_4$) and concentrated. The residue was analyzed by NMR, ir, and GLC comparison with authentic samples. Results are summarized in Tables I and II.

Registry No.—Potassium cyanate, 590-28-3; HF, 7664-39-3; potassium thiocyanate, 333-20-0.

References

(1) G. A. Olah, "Friedel-Crafts Chemistry", Wiley, New York, N. Y., 1972.
(2) L. Gattermann, *Justus Leibigs Ann. Chem.*, **244**, 29 (1888).
(3) F. H. Runge, F. H. Reinhardt, and G. Kuhnhanss, *Chem. Tech. (Berlin)*, **8**, 644 (1956); H. Hopff, German Patent 584,142 (1933); *Chem. Abstr.*, **28**, 174 (1934).
(4) V. P. Lopatinskii and V. V. Goldstein, Russian Patent 375,516 (1972).
(5) M. Linhard and K. Betz, *Chem. Ber.*, **73**, 177 (1940); also see G. D. Buckley, H. A. Piggott, and A. J. E. Welch, *J. Chem. Soc.*, 864 (1945).
(6) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969, p 34.
(7) "CRC Handbook of Chemistry and Physics", 48th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967.
(8) K. C. Joshi and S. Giri, *J. Indian Chem. Soc.*, **37**, 423 (1960).
(9) S. Kakimoto, J. Seydel, and E. Wempe, *Arzneim.-Forsch.*, **12**, 127 (1962).
(10) E. C. Taylor and J. A. Zoltewicz, *J. Am. Chem. Soc.*, **82**, 2656 (1960).
(11) C. M. Sharts and W. A. Sheppard, *Org. React.*, **21**, 220 (1974).

Synthesis of Tertiary Amines by Selective Diborane Reduction

Pamela L. Russ and Edward A. Caress*

Department of Chemistry, The George Washington University, Washington, D.C. 20052

Received September 5, 1975

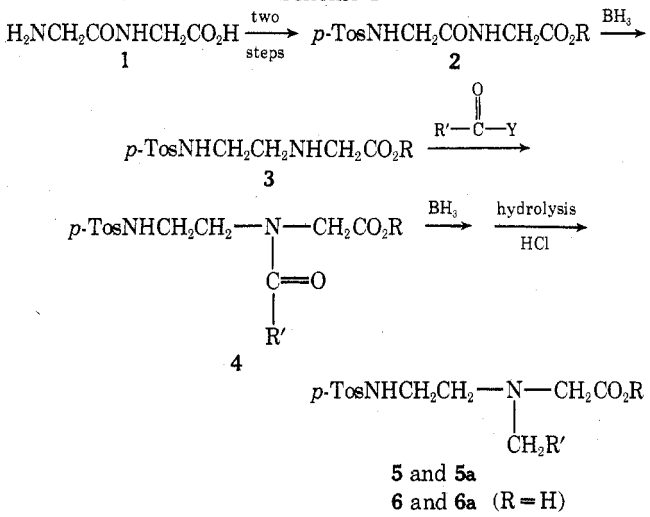
The preparation of tertiary amines containing functionality in the substituent groups has frequently presented a challenge to the synthetic organic chemist. A survey of the literature shows that there are few methods of preparing such tertiary amines and that many of them have limited scope, or poor yield, or both.[1] For example, the reduction of N,N-disubstituted amides with lithium aluminum hydride is one of the more common methods of preparing tertiary amines. The use of this reagent rather severely limits the type of functionality that can be permitted elsewhere in the amide. Also, an aldehyde is often obtained instead of, or along with, the desired amine.[2]

During the past 15 years, diborane has been developed as a reagent for reducing a variety of functional groups.[3] Its usefulness lies in the property that, while most functional groups can be reduced with the reagent, the rates of reduction vary greatly. This permits the reduction of certain groups in a polyfunctional molecule while leaving others intact, if conditions are properly chosen. The relative activity of diborane toward different functional groups is carboxylic acids and amides > olefins > ketones > nitriles > epoxides > esters > acid chlorides.[4] This order of reactivity suggests the possibility of reducing an amide with diborane to obtain an amine while leaving a variety of other functional groups untouched. Thus, with proper protection of a carboxyl function, an amide can be reduced to an amine that carries the carboxyl function.

The purpose of this paper is to suggest a new general approach, shown in Scheme I, to the synthesis of polyfunctional tertiary amines and to report the synthesis of *N*-ethyl-*N*-(2-tosylaminoethyl)glycine hydrochloride (**6a**) using this approach.

In the synthesis of **6a**, the starting material was glycylglycine 1 and it is necessary to protect both the amine and the carboxylic acid functions of this molecule. The amine function was protected by the tosyl group as the tosylamide is known to be inert to diborane reduction.[5] The choice of protecting group for the carboxyl function posed a greater problem.

Scheme I



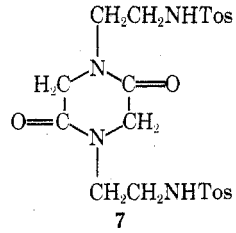
1 2 3 4 5 and 5a 6 and 6a (R = H)

R = pentachlorophenyl, R′ = methyl
Y = acetoxy, a = hydrochloride salt

There are at least two reports of the use of diborane to reduce selectively amido esters[6] or peptides.[7] In the amido ester case, although monoreduction products (amino esters) were obtained, considerable amounts of completely reduced products were found. In the peptide case, the reagent was found to be unsatisfactory because in addition to obtaining the desired material, complete reduction of the peptide occurred and cyclic by-products also were found. In order to prepare a compound such as **5**, it appeared necessary to determine if it was possible to prepare an ester which would be inert to reduction by diborane while the amide was being reduced.

A preliminary investigation of several *N*-tosylglycine esters (ethyl, *tert*-butyl, triphenylmethyl, *p*-nitrophenyl, pentachlorophenyl) indicated that only the pentachlorophenyl ester was stable to excess diborane at room temperature and at 66°, giving no reduction to the *N*-tosylamino alcohol. The ester **2** was prepared from *N*-tosylglycylglycine and pentachlorophenol using dicyclohexylcarbodimide (DDC) as the coupling agent.[8] It was then treated with diborane using a one-hydride excess of BH_3 (calculated on the basis of reduction of amide carbonyl only). At room temperature there was no reduction of the amide carbonyl of **2**, but in refluxing tetrahydrofuran (THF), bp 66°, the amide carbonyl reduced readily to give **3** which was obtained as its relatively insoluble hydrobromide salt in 90% yield (crude). No completely reduced material (the amino alcohol) was found in the reaction mixture.

In the preparation of the *N*-acylamine **4** a problem arose because a diketopiperazine, **7**, formed very easily when **3**



7

was treated with triethylamine or when the free base of **3** was treated with acetic anhydride. To prevent the formation of **7** the free base was acylated without purification and the acetic anhydride was carefully distilled before use. Compound **4** was also unstable, giving **7**, and could not be easily purified.

The amide carbonyl in **4** was readily reduced with diborane at room temperature in excellent yield. Both the hydrochloride salt **6a** and the ester hydrochloride sale **5a** were obtained and were easily separated. Increasing the amount of 6 *N* hydrochloric acid used to decompose the reaction did not seem to change the ratio of **5a** to **6a**. The ester **5** was converted to **6** in near-quantitative yield, 98%, by saponification with sodium hydroxide.

These experimental results show that it is possible to reduce selectively an amide carbonyl in a compound containing both a protected amine and a protected carbonyl group. We suggest that the results from the second reduction (**4** → **5**) indicate that the proper choice of an acylating agent should allow the introduction of a third functional group into a tertiary amine. This would give a tertiary amine containing an amine function in one substituent, a carboxylic acid function in the second, and the third substituent group could contain another functionality unaffected by diborane or else it could be an alkyl group, as it is in the present case.

Experimental Section

General Methods. Thin layer chromatography (TLC) was carried out on Eastman silica gel chromatogram sheets with fluorescent indicator. NMR spectra were obtained using a Varian A-60 spectrometer or a Hitachi Perkin-Elmer R-20 high resolution NMR spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Ir spectra were obtained using either a Perkin-Elmer 457 or 521 spectrophotometer. Mass spectra were obtained on a Perkin-Elmer 270 mass spectrometer. Solvents were dried over 3A molecular sieves. All melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The 1 *M* BH_3–THF was purchased from Ventron Corp. and used as obtained. Elemental analyses were obtained by Galbraith Laboratories, Inc. All other chemicals were used as received unless otherwise indicated.

***N*-Tosylglycylglycine.** Tosyl chloride (24.4 g, 0.13 mol) was added in portions with stirring over 0.75 hr to a mixture of glycylglycine (15 g, 0.11 mol), triethylamine (36.6 ml, 0.29 mol), 180 ml of water, and 90 ml of tetrahydrofuran (THF). After the mixture had been stirred for 3 hr at room temperature, the THF was removed in vacuo. The solution was extracted with four 100-ml portions of ether. The aqueous layer was acidified with 12 *N* hydrochloric acid and extracted with three 200-ml portion of ethyl acetate. The extracts were combined, dried over $MgSO_4$, filtered, and reduced in volume. The white solid was filtered, washed with ethyl acetate, and air dried to give 30.3 g of *N*-tosylglycylglycine (85%, mp 172–173.5°, lit. mp 178–179° [9]): ir (Nujol) 3350, 3250, 1725, 1620 cm^{-1}; NMR (Me_2SO-d_6) 2.35 (s, 3, CH_3Ar), 3.40 (d, 2, J = 7 Hz, $(CNCH_2)$), 3.69 (d, 2, J = 7 Hz, $SNCH_2$), 7–8.1 ppm (m, 6, Ar, both NH).

***N*-Tosylglycylglycine Pentachlorophenyl Ester (2).** DCC (5.55 g, 0.027 mol) was added to a stirred mixture of *N*-tosylglycylglycine (7.7 g, 0.027 mol) and pentachlorophenol (7.17 g, 0.027 mol) in 200 ml of dry THF with cooling. The reaction mixture was stirred and kept cold for 2 hr and then stirred at room temperature for several days. The reaction mixture was heated to the boiling point, filtered, and refiltered several times through the same funnel to remove the DCC. The filtrate was reduced in volume, diluted with ether, and cooled to give 3.0 g of ester **2**: mp 190–193° dec; ir (Nujol) 3390, 3300, 1775, 1680 cm^{-1}. Further cooling of the filtrate gave 6.4 g of additional ester, mp 210–214° dec, for a total crude yield of 87%. Recrystallization of the combined materials by dissolving them in warm DMF and subsequent filtration into a large volume of ether gave 8.9 g of the ester (64%, mp 204–205° dec).

An analytical sample was prepared by recrystallization from dimethylformamide–ether: mp 210–211° dec; NMR (Me_2SO-d_6) 2.38 (s, 3, CH_3Ar), 3.56 (d, 2, J = 7 Hz, $CNCH_2$), 4.38 (d, 2, J = 7 Hz, $SNCH_2$), 7.32–8.2 (m, 5, Ar, NH), 8.64 ppm (t, 1, J = 6 Hz, NH). Anal. Calcd for $C_{17}H_{13}Cl_5N_2O_5S$ (534.66): C, 38.19; H, 2.45; Cl, 33.16; N, 5.24; S, 6.00. Found: C, 38.15; H, 2.48; Cl, 32.98; N, 5.21; S, 6.24.

***N*-(2-Tosylaminoethyl)glycine Pentachlorophenyl Ester (3).** The experimental apparatus consisted of a three-neck round-bottom flask fitted with a nitrogen inlet, dropping funnel, and con-

denser with drying tube. The reaction mixture was stirred magnetically. All additions were done at ice-bath temperatures and all reactions were carried out under a nitrogen atmosphere.

To the ester **2** (6.2 g, 11.6 mol) suspended in 300 ml of dry THF was added 1 *M* BH_3–THF (20 ml, 20 mmol) in 20 ml of dry THF as rapidly as possible. The reaction mixture was refluxed for 1.5 hr and cooled in an ice bath and 50 ml of acetic acid saturated with HBr(g) was added dropwise. The reaction was stirred at room temperature for 1 hr and filtered to give 5.0 g of the reduced ester **3** HBr, mp 196–197° dec. Reduction in volume of the filtrate and dilution with ether gave an additional 1.6 g of **3** HBr: mp 193–194° dec; 96% total crude yield; ir (Nujol) 3250, 1800 cm^{-1}; NMR (Me_2SO-d_6) 2.43 (s, 3, CHAr), 3.22, 4.00, 4.74 (a series of three singlets which change such that the singlet at 4.74 decreases, the singlet at 4.00 increases, and the singlet at 3.22 becomes a multiplet, as the ester reacts with Me_2SO-d_6, 6, CH_2N), 7.46 and 7.84 (d, 2, J = 9 Hz, Ar), 8.00 (s, 1, $NHSO_2$), 9.4 ppm (s, 2, NH_2^+).

An analytical sample was prepared by recrystallization from a mixture of dimethylformamide–THF–ether to give the pure ester **3** HBr, mp 196.5–197° dec. Anal. Calcd for $C_{17}H_{15}Cl_5N_2O_4S$·HBr (601.60): C, 33.94; H, 2.68; Br, 13.28; Cl, 29.47; S, 5.33. Found: C, 33.84; H, 2.58; Br, 13.43; Cl, 29.57; S, 5.43.

Triethylamine (1.25 ml, 9 mmol) in 75 ml of dry chloroform was added to a stirred suspension of **3** HBr (5.4 g, 9 mmol) in 75 ml of dry chloroform. The reaction mixture was stirred until solution occurred and then concentrated to dryness in vacuo. The residue was warmed gently with 200 ml of benzene and the triethylamine hydrobromide was removed by filtration. The benzene filtrate was concentrated in vacuo to 50 ml to give 4.0 g of the free base **3** (85%, mp 123–125°): ir (Nujol) 3300, 3140, 1785 cm^{-1}.

The free base was unstable and formed the diketopiperazine **7** on attempted purification. A sample of **7** was recrystallized from ethanol–dimethylformamide to give a solid: mp 251–252°; ir (Nujol) 3260, 1635 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_4O_6S_2$ (**7**) (508.63): C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.96; H, 5.45; N, 11.05; S, 12.77.

***N*-Acetyl-*N*-(2-tosylaminoethyl)glycine Pentachlorophenyl Ester (4).** The base **3** (3.9 g, 7.5 mmol) was stirred in redistilled acetic anhydride (25 ml) until solution occurred. The reaction mixture was then stirred for an additional 2 hr at room temperature. A solid precipitated. The solid was filtered and washed with a small portion of acetic anhydride and then with ether to give 3.0 g of **4** (73%, mp 147–148°): ir (Nujol) 3140, 1786, 1645 cm^{-1}.

***N*-Ethyl-*N*-(2-tosylaminoethyl)glycine Hydrochloride (6a).** The amido ester **4** (1.1 g, 3 mmol) in 40 ml of dry THF was added dropwise to 1 *M* BH_3–THF (3.4 ml, 3.4 mmol) in 15 ml of cold, dry THF. The reaction mixture was stirred at room temperature for 2 hr and then cooled in an ice bath. Hydrochloric acid (0.5 ml, 6 *N*) was added dropwise and the reaction mixture stirred for 1 hr. The solid was filtered and washed with THF to give 0.2 g of the amino acid salt **6a**, mp 154–160° dec. Reduction in volume of the filtrate and dilution with ether gave 0.15–0.20 g more of **6**: ir (Nujol) 3300 (broad), 3060, 1730 cm^{-1}.

The filtrate was concentrated in vacuo. The residue was dissolved in a small volume of THF and diluted with ether to remove the pentachlorophenol. The material that was insoluble in ether was treated with a small portion of THF to give 0.15 g of the amino ester **5**: mp 134–136° dec; ir (Nujol) 3210, 1795 cm^{-1}. Reduction of the filtrate and treatment of the residue with THF–ether gave about 0.1 g of crude **5**.

The amino ester **5** (0.45 g, 0.77 mmol) was saponified with sodium hydroxide (1.54 ml, 1.54 mmol) to give both the amino acid salt **6a**, 0.2 g, ir (Nujol) 1730 cm^{-1}, contains sodium chloride (theory for NaCl 80 mg), and the free amino acid **6**, mp 185–187°, ir (Nujol) 3010, 1650 cm^{-1}, which is a 98% recovery of the material based on recovery of the amino acid salt **6a**.

An analytical sample of **6a** was prepared by recrystallization from 2-propanol: mp 155–161°; ir (Nujol) 3300 (broad), 3050, 1730 cm^{-1}; NMR (Me_2SO-d_6) 1.23 (t, 3, J = 8 Hz, CH_3CH_2), 2.42 (s, 3, CH_3Ar), 3.25 (m, 6, CH_2N), 3.8 (broad t) and 4.1 (s, 2, NCH_2CO), 7.42 and 7.78 (d, 2, J = 9 Hz, Ar), 8.22 ppm (s, 1, SNH). Anal. Calcd for $C_{13}H_{21}N_2O_4ClS$ (336.83): C, 46.36; H, 6.28; Cl, 10.53; N, 8.32; S, 9.52. Found: C, 46.19; H, 6.34; Cl, 10.39; N, 8.28; S, 9.53.

Acknowledgment. The authors wish to thank Dr. Ralph C. Northrup of Microbiological Associates, Inc., for his encouragement and helpful discussions.

Registry No.—**1**, 556-50-3; **2**, 57066-12-3; **3**, 57066-13-4; **3** HBr, 57066-14-5; **4**, 57066-15-6; **5**, 57066-16-7; **6**, 57066-17-8; **6a**, 57066-18-9; **7**, 57066-19-0; acetic anhydride, 108-24-7; tosyl chloride, 98-59-9; *N*-tosylglycylglycine, 4703-34-8; pentachlorophenol, 87-86-5.

References and Notes

(1) (a) C. Buehler and D. Pearson, "Survey of Organic Syntheses", Wiley-Interscience, New York, N.Y., 1970, pp 413–507; (b) I. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Wiley-Interscience, New York, N.Y., 1971, pp 230–266; (c) J. March, "Advanced Organic Chemistry; reactions, Mechanisms and Structure", McGraw-Hill, New York, N.Y., 1969; (d) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry", W. A. Benjamin, New York, N.Y., 1964, pp 652–663.
(2) Reference 1a, p 421.
(3) (a) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786–2792 (1973); (b) H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912–916 (1973); (c) H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637–1646 (1960); (d) H. C. Brown and P. Heim, *Ibid.*, **86**, 3566–3567 (1964); (e) H. C. Brown and B. C. Subba Rao, *Ibid.*, **82**, 681–686 (1960).
(4) C. F. Lane, *Aldrichimica Acta*, **6**, 21–34 (1973).
(5) J. P. Greenstein and M. Wintlz, "Chemistry of the Amino Acids", Vol. 2, Wiley, New York, N.Y., 1961, p 886.
(6) M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, **33**, 3637–3639 (1968).
(7) O. Yonemitsu, T. Hamad, and Y. Kanaoka, *Tetrahedron Lett.*, 3575–3578 (1968).
(8) Reference 5, pp 1016–1023.
(9) Reference 5, p 1027.

Photoreduction of Substituted Benzo[*b*]furans by Aliphatic Amines

Cyril Párkányi*

Department of Chemistry, The University of Texas at El Paso, El Paso, Texas 79968

Alain Lablache-Combier,* I. Marko, and Harry Ofenberg[1]

Laboratoire de Chimie Organique Physique, Université des Sciences et Techniques de Lille, B. P. 36, F-59650 Villeneuve d'Ascq, France

Received June 27, 1975

In one of our previous papers we have reported that uv irradiation (254 nm) of benzo[*b*]thiophene in aliphatic amines leads to the corresponding adducts and we have postulated the intermediate formation of an exciplex.[2] In contrast to benzo[*b*]thiophene, no detectable reaction was observed when benzo[*b*]furan was irradiated with uv light in an aliphatic amine.[2] Assuming that the photoexcited heterocycle reacts with the amine via intermediate formation of an exciplex[3,4] in which the heteroaromatic derivative possesses the character of a radical anion, we were able to explain the difference in the photochemical behavior of these two heterocycles as due to the fact that the maximum spin density in the benzo[*b*]furan radical anion is found in the 4 position whereas in the benzo[*b*]thiophene radical anion it is the 2 position where the spin density is the highest.[2] This means that, if a photoreaction between benzo[*b*]furan and an aliphatic amine, HNR_2, were possible, it would lead to the formation of product **1** which would be unstable under the conditions used in our study.[2]

To verify this assumption, we have synthesized some benzo[*b*]furan derivatives in which the spin density of their radical anion is the highest in the 4 position, and we have also prepared some other derivatives whose radical anions have the highest spin density in the 2 position. According to our hypothesis, the former group of compounds should not give any isolable products when irradiated in an aliphatic amine, whereas uv irradiation of the compounds belonging to the latter group is expected to lead to the formation of stable photoproducts.