The Triazene Moiety as a Protecting Group for Aromatic Amines[1]

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Reaction of (2-, (3-, and (4-bromophenyl)-3,3-(1,4-butanediyl)triazenes (derived from the corresponding 2-, 3-, and 4-bromoanilines) with *sec*- or *tert*-butyllithiums gave the corresponding (triazenylaryl)-lithiums; these intermediates reacted with a variety of electrophiles to give substituted aryl triazenes. These products cound be converted to substituted anilines by reduction or to novel substituted aromatics by a modified Sandmeyer reaction.

Introduction

Although the first investigations of the metallation of anilines were reported some 50 years ago by Gilman, et al., no general methodology for the preparation of ortho-, meta- and para-substituted primary aniline derivatives via the corresponding lithio derivatives has appeared in the chemical literature to date. Gilman's 2-lithioaniline di- (or tri-) anion generated by direct deprotonation of aniline with *n*-butyllithium gave anthranilic acid in only 4.2% yield after carbonation of the intermediate anion.[2] Other experiments established halogen–lithium exchange as a more efficient method for the formation of such anions, carbonation of the anion formed by reaction of *n*-butyllithium with 2-bromoaniline gave anthranilic acid in 36% yield.[3] In similar fashion, meta- and para-anions derived from 3- and 4-bromo-*N*,-*N*-dimethylanilines gave the corresponding *m*- and *p*-dimethylaminobenzoic acid derivatives in 26 and 41% yields, respectively, but the primary aniline derivatives were not reported by this route.[4]

In recent years, procedures for the directed metallation at the ortho position of aniline derivatives have been developed in which the directing group also stabilizes the carbanionic intermediate. Thus, phenyl isocyanide,[5] pivalanilide[6] and *N*-(*tert*-butoxycarbonyl)aniline[7] may be deprotonated in the ortho position by lithium bases, reacted with electrophiles, and hydrolyzed to substituted anilines or derivatives thereof. Also, Wender and White reported the preparation of ortho-stabilized dianions from 2-bromoanilides by halogen–lithium exchange and their use for the synthesis of indole derivatives.[8] Thus, site-specific deprotonation and reaction of the intermediate carbanions with a variety of electrophiles has proven to be useful for the synthesis of interesting ortho-substituted aniline derivatives for a variety of synthetic purposes.

Synthesis of primary aniline derivatives by lithiation has been generally limited to those cases producing ortho-substituted compounds. One exception is that recently reproted by Breukelman et al. in which 1-bromo-4-(2,5-dimethylpyrrolyl)benzene was prepared from 4-bromoaniline and subsequently lithiated by halogen–metal exchange prior to reaction with an electrophile. The resulting product could be converted to a 4-substituted aniline by hydrolysis of the 2,5-dimethylpyrrole moiety with hydroxylamine hemichloride.[9]

We needed to prepare a selection of ortho-, meta-, and para-substituted aniline derivatives and sought a general method which would allow the synthesis of these compounds from readily available intermediates. From the above work, it was apparent that the generation of the ortho derivatives should present no problem but, with the exception of the Breukelmann example, we were unaware of any known methodology for the generation of both *m*- and *p*-aminophenyl carbanion equivalents from protected aniline derivatives. Substitution of a nitro group for the amino group in precursor compounds is not a viable alternative since the corresponding *m*- and *p*-nitrophenyl carbanions are known to be highly unstable, only trace amounts of products being derived from the meta-substituted species at −100 °C and none at all from the *p*-nitro species.[10] What was needed was a new aniline protecting group which would be suitable for use with meta- and para-carbanions, which would be stable to a variety of electrophilic reagents, and which could be formed and removed in high yield under mild conditions.

Results and Discussion

Aryltriazenes have been known for many years[11,12] and are generally crystalline compounds which are stable to both air, light, and basic conditions.[13] It appeared to us that the triazene moiety should be useful for the protection of an aromatic amine moiety during the generation of an aromatic carbanion elsewhere in the ring, i.e. by metal–halogen exchange and during the subsequent reaction of this carbanion with a variety of electrophiles. We anticipated that no directing effect would be likely due to the diazo nature of the derivatized aniline nitrogen atom, products in this case being derived from unstabilized monoanions. The potential utility of this group was further enhanced by the fact that triazenes have been converted to their corresponding anilines by reduction under mile conditions.[14,15]

Furthermore, aryltriazenes have been known for many years to be useful intermediates for the synthesis of aryl

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(2) Gilman, H.; Brown, G. E.; Webb, F. J.; Spatz, S. M. *J. Am. Chem. Soc.* **1940**, *62*, 977.
(3) Gilman, H.; Langham, W.; Willis, H. R. Ibid. **1940**, *62*, 346.
(4) Gilman, H.; Banner, I. Ibid. **1940**, *62*, 344.
(5) Walborsky, H. M.; Ronman, P. *J. Org. Chem.* **1978**, *43*, 731.
(6) Fuhrer, W.; Gschwend, H. W. Ibid. **1979**, *44*, 1133.
(7) Muchowski, J. M.; Venuti, M. C. Ibid. **1980**, *45*, 4798.
(8) Wender, P. A.; White, A. W. *Tetrahedron Lett.* **1981**, *22*, 1475.
(9) Breukelman, S. P.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Chem. Commun.* **1982**, 800.
(10) Kobrick, G., Buck, P. *Chem. Ber.* **1970**, *103*, 1412.
(11) Wallach, O. *Liebig's Ann. Chem.* **1886**, *235*, 233.
(12) Wallach, O.; Heusler, F. Ibid. **1888**, *243*, 219.
(13) Merkushev, E. B. *Synthesis* **1988**, 923.
(14) Lunn, G.; Sansone, E. B.; Keefer, L. K. *Synthesis* **1985**, 1104.
(15) Keefer, L. K.; Lunn, G. *Chem. Rev.* **1989**, *89*, 459.

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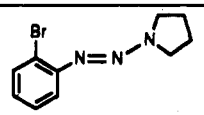
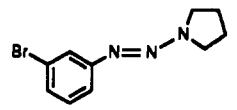
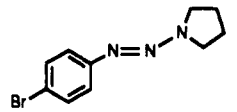
Table I. 2-, 3-, and 4-Bromotriazenes

entry	Triazene	mp (°C)	% yield[a]
1	 **1**	54.5–55.5	88
2	 **2**	58–60	56
3	 **3**	82–84	84

[a] Recrystallized yields.

iodides[13,16] by decomposition to the corresponding diazonium species in the presence of hydriodic acid and have recently been found to be of some utility for the synthesis of other aromatic halides by modifications of these procedures.[17-19]

The synthesis of the previously unreported (2-, (3-, and (4-bromophenyl)- and (3,5-dimethylphenyl)-3,3-(1,4-butanediyl)triazenes **1–3** and **25** was achieved in good yield by diazotization of the corresponding aniline under standard conditions and subsequent reaction of the diazonium salt with pyrrolidine in aqueous KOH.[16] The products which precipitated were easily crystallized from ethanol to give stable, analytically pure crystalline compounds (Table I).

Metalation of these compounds at −78 °C with *sec*- or *tert*-butyllithium yielded the corresponding aryl carbanions which were reacted with electrophiles to give substituted aryltriazenes in good yields as shown in Table II. Thus, carbon dioxide and ketones and aldehydes react to give the corresponding tertiary and secondary alcohols (entries 1, 2, 6–10), silyl and stannyl halides yield the desired arylsilanes and -stannanes (entries 4, 11, and 12) and reaction with a disulfide gave the aryl thioether **7** (entry 3). This procedure may also be useful as an alternative, nonreductive method for the site-specific incorporation of deuterium (or tritium, by analogy) into aniline derivatives (entry 5). The unsubstituted (phenylazo)pyrrolidine **26** was also isolated in those cases where column chromatography was performed; presumably this compound arises from reaction of the anion with adventitious water.

As expected, metal–halogen exchange was the only reaction observed between bromotriazenes and the lithium alkyls; no products from substitution in positions other than that initially substituted with bromine were detected in any of the reaction mixtures. Phenyl-3,3-(1,4-butanediyl)triazene was not lithiated under these conditions and there appeared to be little or no difference in the reactivity of the three types of anions, either as far as the reaction conditions or the rates of reactions with electrophiles, suggesting that the triazenes do not exert any stabilizing effect by coordination such as that reported between amide carbonyl and the ortho position in anilides.[5-8] The triazene moiety appears to be stable under the reaction conditions, since no evidence of decomposition of the anion solutions was noted.

Hydrogenolysis of the triazene derivatives to the corresponding substituted anilines was achieved by stirring the triazene in methanolic potassium hydroxide solution in the presence of nickel–aluminum alloy at room temperature. This procedure gave the anilines in good yields, thus making this three-step procedure of protection, reaction, and deprotection eminently suitable for synthetic purposes. Although isolable, several of the 4′-aminophenyl secondary and tertiary alcohol derivatives did appear to be of limited stability upon chromatography on silica gel.

As mentioned above, aryltriazenes have served as precursors for aryl halides, reacting under acidic conditions in which an intermediate aryldiazonium species is produced. This procedure is particularly useful in the synthesis of radiolabeled compounds in which higher radiochemical yields are obtained starting from the crystalline triazenes.[17-19] We reasoned that this reaction, by analogy with Sandmeyer type of reactions might be useful for the synthesis of other aryl derivatives. The results of these experiments are reported in Table III in which it will be noted that the decomposition of two model triazenes in the presence of copper salts led to the desired substituted aryls. Thus were prepared not only the relatively mundane chloro and bromo derivatives (entries 1, 2, 5, and 6) but also the H-substituted products **29** and **34** (entries 3 and 8), the nitrile (entry 7), and the methyl-substituted benzenes **30** and **35** (entries 4 and 9) from the Pd^0-catalyzed reaction of the diazonium intermediate with tetramethyltin.

In summary, we have discovered a novel and practical method for protecting the aromatic amine functionality in 2-, 3-, and 4-bromoanilines during the formation of the corresponding aryl carbanions by halogen–metal exchange and the reaction of these carbanions with a wide variety of electrophiles. The scope of the reaction seems to be quite broad in that a wide variety of substituents are tolerated by the reaction conditions and a wide variety of electrophiles can be used leading to compounds not easily obtained by other routes. The regeneration of the amines is conveniently performed in high yield by hydrogenolysis or the amine may be converted to other useful functional groups by known methods. The reaction sequence reported herein is not only useful for the synthesis of aniline derivatives but may also be useful for converting a bromo aniline to an aromatic compound substituted stepwise at the two original sites with novel substituents.

CAUTION: Aryldialkyltriazenes have been reported to demonstrate potent carcinogenic activity in rats and have demonstrated a range of mutagenic activities in the Ames test after microsomal activation.[20-22] Preliminary studies in our laboratories have demonstrated that the (*m*-bromophenyl)triazene **2** is positive in the Ames test after metabolic activation although the unactivated species

(16) Foster, N. J.; Heindel, N. D.; Burns, H. D.; Muhr, W. *Synthesis* **1980**, 572.
(17) Tewson, T. J.; Welch, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 1149.
(18) Ku, H.; Barrio, J. R. *J. Org. Chem.* **1981**, *46*, 5239.
(19) Barrio, J. R.; Satyamurthy, N.; Ku, H.; Phelps, M. E. *J. Chem. Soc., Chem. Commun.* **1983**, 443.
(20) Preussmann, R.; Ivankovic, S.; Landschutz, C.; Gimmy, J.; Flohr, E.; Griesbach, U. *Z. Krebsforsch.* **1974**, *81*, 285.
(21) Venger, B. H.; Hansch, C.; Hatheway, G. J.; Amrein, Y. U. *J. Med. Chem.* **1979**, *22*, 473.
(22) Shusterman, A. J.; Debnath, A. K.; Hansch, C.; Horn, G. W.; Fronczek, F. R.; Greene, A. C.; Watkins, S. F. *Mol. Pharmacol.* **1989**, *36*, 939.

does not appear to be active.[23] For this reason, these and other compounds and derivatives including the triazene moiety as part of their structure must be regarded as potentially carcinogenic and appropriate precautions taken to ensure that human contact does not occur.

Experimental Section

CAUTION: Some triazene derivatives are reported to demonstrate potent carcinogenic activity. Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer with internal deuterium lock. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. EI mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. Headspace analyses were performed with a Perkin-Elmer Sigma 2000 gas chromatograph equipped with a Perkin-Elmer HS100 autosampler. The column was a 50 m × 0.25 mm i.d. 5% phenyl methyl silicone (1 μm) with helium as carrier gas.

General Procedure A for the Preparation of [(2-, [(3- and [(4-Bromophenyl)azo]pyrrolidines. [(2-Bromophenyl)azo]-pyrrolidine (1). A solution of 10.0 g (0.058 mol) of 2-bromoaniline in 11.7 mL of concd HCl was cooled in an ice bath while a solution of 4.0 g (0.058 mol) of $NaNO_2$ in 5 mL of cold water was added dropwise. The resulting solution of the diazonium salt was stirred in the cold for 10 min and then added all at once to a chilled solution of 4.54 g (5.33 mL, 0.064 mol) of pyrrolidine in 50 mL of 1 M KOH solution. The reaction mixture was stirred for 30 min in the cold and then the precipitate was isolated by filtration. The damp solid was then recrystallized from about 50 mL of absolute EtOH to give 12.95 g (88%) of the desired product: mp 54.5–55.5 °C; ^{1}H-NMR ($CDCl_3$) δ 2.03 (4 H, broad s, CH_2CH_2), 3.74 (2 H, broad s, CH_2N), 3.92 (2 H, broad s, CH_2N), 6.94 (1 H, t, J = 7, =CH–), 7.21 (1 H, t, J = 7, =CH–), 7.37 (1 H, d, J = 7, =CH–), 7.55 (1 H, d, J = 7, =CH–); MS M^+ = 253/255; $(M - C_4H_8N)^+$ = 183/185; $(M - C_4H_8N - N_2)^+$ = 155/157. Anal. Calcd for $C_{10}H_{12}N_3Br$ (254.14): C, 47.26; H, 4.73; N, 16.54. Found: C, 47.03; H, 4.76; N, 16.68.

[(3-Bromophenyl)azo]pyrrolidine (2) was prepared from 3-bromoaniline according to general procedure A in 56% yield: mp 59–60 °C; ^{1}H-NMR ($CDCl_3$) δ 2.00 (4 H, broad s, CH_2CH_2), 3.66 (2 H, broad s, CH_2N), 3.84 (2 H, broad s, CH_2N), 7.08–7.22 (2 H, m, =CH–), 7.29 (1 H, d, J = 7, =CH–), 7.56 (1 H, s, =CH–); MS M^+ = 253/255; $(M - C_4H_8N)^+$ = 183/185; $(M - C_4H_8N - N_2)^+$ = 155/157. Anal. Calcd for $C_{10}H_{12}N_3Br$ (254.14): C, 47.26; H, 4.73; N, 16.54. Found: C, 47.20; H, 4.38; N, 16.34.

[(4-Bromophenyl)azo]pyrrolidine (3) was prepared from 4-bromoaniline according to general procedure A in 84% yield: mp 82–84 °C; ^{1}H-NMR ($CDCl_3$) δ 2.02 (4 H, broad s, CH_2CH_2), 3.77 (4 H, broad s, CH_2NCH_2), 7.27 (2 H, d, J = 7, =CH–), 7.41 (2 H, d, J = 7, =CH–); MS M^+ = 253/255; $(M - C_4H_8N)^+$ = 183/185; $(M - C_4H_8N - N_2)^+$ = 155/157. Anal. Calcd for $C_{10}H_{12}N_3Br$ (254.14): C, 47.26; H, 4.73; N, 16.54. Found: C, 47.16; H, 4.60; N, 16.55.

[(3,5-Dimethylphenyl)azo]pyrrolidine (25) was prepared from 3,5-dimethylaniline according to general procedure A in 71% yield: mp 50–51 °C; ^{1}H-NMR ($CDCl_3$) δ 1.94 (4 H, m, CH_2CH_2), 2.28 (6 H, s, CH_3, CH_3), 3.74 (4 H, broad s, CH_2NCH_2), 6.73 (1 H, s, =CH–), 6.99 (2 H, s, =CH–); MS M^+ = 203; $(M - C_4H_8N)^+$ = 133; $(M - C_4H_8N - N_2)^+$ = 105. Anal. Calcd for $C_{12}H_{17}N_3$ (203.28): C, 70.90; H, 8.43; N, 20.67. Found: C, 70.85; H, 8.41; N, 20.83.

General Procedure B for the Preparation of Substituted (Phenylazo)pyrrolidines. [[4-(Trimethylsilyl)phenyl]azo]-pyrrolidine (15). A solution of 1.0 g (3.9 mmol) of [(4-bromophenyl)azo]pyrrolidine (3) in 30 mL of anhydrous ether was cooled to −78 °C in a flame-dried flask under dry N_2. The temperature of the reaction mixture was held below −65 °C while 6.6 mL of 1.3 M *sec*-butyllithium in hexane (8.6 mmol) was added dropwise to give a dark red solution of the anion. After 30 min at −78 °C, 1.25 mL (1.07 g, 8.9 mmol) of trimethylsilyl chloride was added and the reaction mixture was allowed to warm to room temperature overnight. The resulting solution was partitioned between water and ether and extracted with ether. The combined ether extracts were dried and the solvent was evaporated to yield the crude triazene. Column chromatography on silica gel eluted with hexane/ethyl acetate mixtures gave the pure product in 60% yield: mp 84–85 °C; the analytical sample was sublimed at 65–68 °C (oil bath)/0.1 mm; ^{1}H-NMR ($CDCl_3$) δ 0.19 (9 H, s, $Si(CH_3)_3$), 1.96 (4 H, broad s, CH_2CH_2), 3.72 (4 H, broad s, CH_2NCH_2), 7.29 (2 H, d, J = 7, =CH–), 7.40 (2 H, d, J = 7, =CH–); MS M^+ = 247; $(M - C_4H_8N)^+$ = 177; $(M - C_4H_8N - N_2)^+$ = 149. Anal. Calcd for $C_{13}H_{21}SiN_3$ (247.41): C, 63.11; H, 8.56; N, 16.98. Found: C, 62.35; H, 8.74; N, 16.79.

2-(Pyrrolidin-1-ylazo)benzoic acid (4) was prepared according to general procedure B by quenching the anion derived from [(2-bromophenyl)azo]pyrrolidine (1) with CO_2 gas while allowing the reaction mixture to warm from −78 °C to room temperature. The reaction mixture was poured onto ice and the pH was adjusted to 5. The solid which separated was filtered and air-dried to give the desired product in 48% yield: mp 123–125 °C; ^{1}H-NMR ($CDCl_3$) δ 2.00–2.22 (4 H, m, CH_2CH_2), 3.68 (2 H, t, J = 7, CH_2N), 4.06 (2 H, t, J = 7, CH_2N), 7.22 (1 H, t, J = 7, =CH–), 7.46 (1 H, t, J = 7, =CH–), 7.65 (1 H, d J = 7, =CH–), 8.20 (1 H, d, J = 7, =CH–); MS M^+ = 219; $(M - OH)^+$ = 202; $(M - C_4H_8N)^+$ = 149; $(M - C_4H_8N - N_2)^+$ = 121. Anal. Calcd for $C_{11}H_{13}N_3O_2$ (219.23): C, 60.26; H, 5.98; N, 19.17. Found: C, 59.88; H, 5.60; N, 18.95.

1-Phenyl-1-[(2-pyrrolidin-1-ylazo)phenyl]ethanol (5) was prepared according to general procedure B by quenching the anion derived from [(2-bromophenyl)azo]pyrrolidine (1) with acetophenone at −78 °C and allowing the reaction mixture to warm to room temperature overnight. After partitioning between water and ether, the ethereal extracts were dried and evaporated and the residues were chromatographed on silica gel with hexane as eluent to give 5: mp 134–135 °C (hexane/EtOAc); ^{1}H-NMR ($CDCl_3$) δ 1.85 (3 H, s, CH_3), 1.91 (4 H, broad s, CH_2CH_2), 3.22 (1 H, broad s, CHN), 3.44 (1 H, broad s, CHN), 3.77 (2 H, broad s, CHN, CHN), 6.91 (1 H, s, =CH–), 7.03–7.32 (6 H, m, =CH–), 7.44 (2 H, t, J = 7, =CH–); MS M^+ = 295; $(M - OH)^+$ = 278; $(M - C_4H_8N)^+$ = 225; $(M - C_4H_8N - N_2)^+$ = 197. Anal. Calcd for $C_{18}H_{21}N_3O$ (295.37): C, 73.19; H, 7.17; N, 14.23. Found: C, 72.63; H, 7.11; N, 14.38.

1-[2-(Phenylthio)phenyl]-2-(pyrrolidin-1-yl)diazene (6) was prepared according to general procedure B by quenching the anion derived from [(2-bromophenyl)azo]pyrrolidine (1) with phenyl disulfide. Chromatography on silica gel using 10:1 hexane/EtOAc gave 6 as an oil in 70% yield: ^{1}H-NMR ($CDCl_3$) δ 1.92 (4 H, broad s, CH_2CH_2), 3.58 (2 H, broad s, CH_2N), 3.82 (2 H, broad s, CH_2N), 6.83 (1 H, t, J = 7, =CH–), 6.88 (1 H, t, J = 7, =CH–), 7.04 (1 H, t, J = 7, =CH–), 7.14–7.46 (6 H, m =CH–); MS M^+ = 283; $(M - C_4H_8N)^+$ = 213; $(M - C_4H_8N - N_2)^+$ = 185; high resolution mass spectrum calcd 283.1143, found 283.1131.

1-[2-(Trimethylsilyl)phenyl]-2-(pyrrolidin-1-yl)diazene (7) was prepared according to general procedure B by quenching the anion derived from [(2-bromophenyl)azo]pyrrolidine (1) with chlorotrimethylsilane. Chromatography on silica gel using hexane as eluent gave 7 as an oil in 91% yield: ^{1}H-NMR ($CDCl_3$) δ 0.28 (9 H, s, $Si(CH_3)_3$), 2.00 (4 H, broad s, CH_2CH_2), 3.74 (4 H, broad s, CH_2NCH_2), 7.04 (1 H, t, J = 7, =CH–), 7.24 (1 H, t, J = 7, =CH–), 7.38 (1 H, d, J = 7, =CH–), 7.44 (1 H, d, J = 7, =CH–); MS M^+ = 247; $(M - CH_3)^+$ = 232; $(M - C_4H_8N - N_2)^+$ = 149; high resolution mass spectrum calcd 247.1505, found 247.1497.

[(3-Deuterophenyl)azo]pyrrolidine (8) was prepared according to general procedure B by quenching the anion derived from [(3-bromophenyl)azo]pyrrolidine (2) with D_2O. The product was extracted from the aqueous mixture with ethyl acetate and crystallized from ethanol to give 8 in 88% yield: mp 51.5–53.0 °C; ^{1}H-NMR ($CDCl_3$) δ 1.91 (4 H, broad s, CH_2CH_2), 3.68 (4 H, broad s, CH_2NCH_2), 6.99 (1 H, d, J = 7, =CH–), 7.13 (1 H, s, =CH–), 7.20 (1 H, t, J = 7, =CH–), 7.28 (1 H, d, J = 7, =CH–); MS M^+ = 176; $(M - C_4H_8N)^+$ = 106; $(M - C_4H_8N - N_2)^+$ = 78.

2-[3-(Pyrrolidin-1-ylazo)phenyl]propan-2-ol (9) was prepared according to general procedure B by quenching the anion

(23) Dr. H. E. Holden, personal communication.

Table II. Reaction of Triazenes with Electrophiles and Cleavage of Products

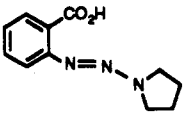
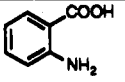
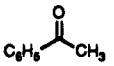
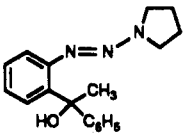
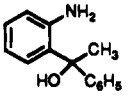
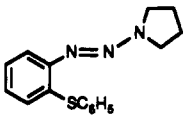
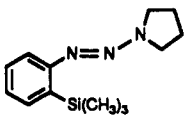
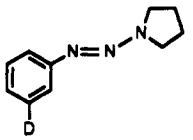
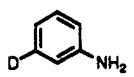
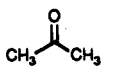
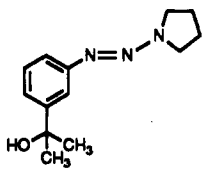
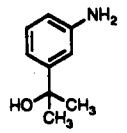
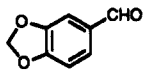
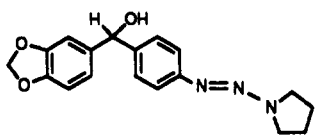
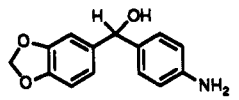
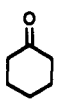
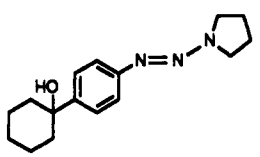
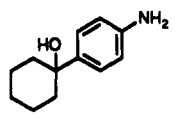
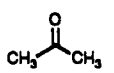
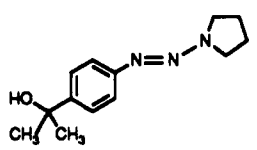
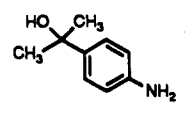
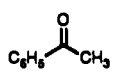
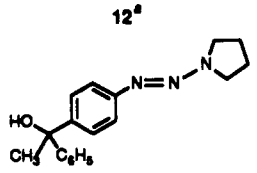
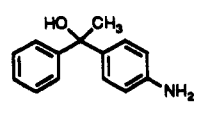
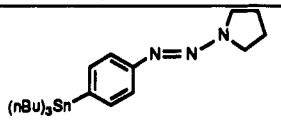
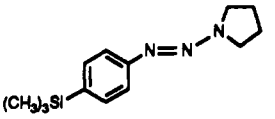
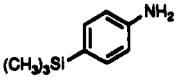
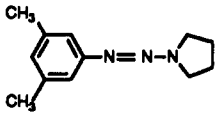
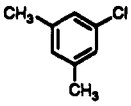
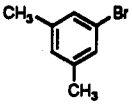
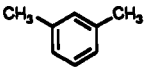
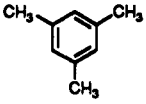
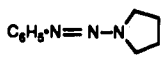
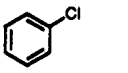
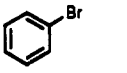
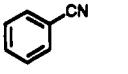
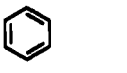
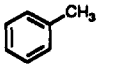
entry	triazene	electrophile	triazene product (% yield)	aniline product (% yield)
1	1	CO_2	 **4** (48)	 **16** (37)
2	1		 **5** (62)	 **17** (64)[b]
3	1	$C_6H_5SSC_6H_5$	 **6** (70)	
4	1	$(CH_3)_3SiCl$	 **7** (91)	
5	2	D_2O	 **8** (88)	 **18** (55)[b]
6	2		 **9** (67)	 **19** (68)
7	3		 **10**[a]	 **20** (42)
8	3		 **11**[a]	 **21** (45)
9	3		 **12**[a]	 **22** (48)
10	3		 **13**[a]	 **23** (49)

Table II (Continued)

entry	triazene	electrophile	triazene product (% yield)	aniline product (% yield)
11	3	$(nBu)_3SnCl$	 **14 (58)**	
12	3	$(CH_3)_3SiCl$	 **15 (60)**	 **24 (38)**[b]

[a] This product was not isolated due to instability to column chromatography. [b] Isolated as the HCl salt.

Table III. Conversion of Model Triazenes to "Sandmeyer" Products

entry	triazene	reactants	product[a]	% yield
1	 **25**	CuCl, HCl	 **27**	54[b]
2	25	CuBr, HBr	 **28**	37[b]
3	25	H_3PO_2, Cu_2O	 **29**	28[b]
4	25	$Sn(CH_3)_4$, $Pd(OAc)_2$	 **30**	25[b]
5	 **26**	CuCl, HCl	 **31**	90[c]
6	26	CuBr, HBr	 **32**	75[c]
7	26	CuCN, NaCN, HCl	 **33**	72[c]
8	26	H_3PO_2, Cu_2O	 **34**	65[c]
9	26	$Sn(CH_3)_4$, $Pd(OAc)_2$	 **35**	40[c]

[a] Products identical with known reference samples. [b] Isolated distilled yield. [c] Yield by head space analysis.

derived from [(3-bromophenyl)azo]pyrrolidine (2) with acetone. Chromatography on silica gel using 1:1 CH_2Cl_2/EtOAc as eluent gave **9** as an oil in 67% yield: ^{1}H-NMR ($CDCl_3$) δ 1.52 (6 H, s, CH_3), 1.94 (4 H, broad s, CH_2CH_2), 3.69 (4 H, broad s, CH_2NCH_2), 7.14–7.26 (3 H, m, =CH-), 7.41 (1 H, s, =CH-); MS M^+ = 233; $(M - OH)^+$ = 216; $(M - C_4H_8N)^+$ = 163; $(M - C_4H_8N - N_2)^+$ = 135; high resolution (FAB) mass spectrum calcd 234.1606, found 234.1622.

Benzo[1,3]dioxol-5-yl-[4-(pyrrolidin-1-ylazo)phenyl]methanol (10) was prepared according to general procedure B by quenching the anion derived from [(4-bromophenyl)azo]pyrrolidine (3) with piperonal. This product was not stable to chromatography on silica gel but was of sufficient purity for use in the subsequent reaction to form compound **20**. The formation of the desired product **10** (contaminated by **26** and unreacted piperonal) was inferred from the ^{1}H-NMR of the crude material: ^{1}H-NMR ($CDCl_3$) δ 1.96 (4 H, broad s, CH_2CH_2), 3.70 (4 H, broad s, CH_2NCH_2), 5.66 (1 H, s, CH), 3.84 (2 H, s, OCH_2O), 6.62–6.78 (3 H, m, =CH-), 7.14–7.32 (4 H, m, =CH-).

1-[4-(Pyrrolidin-1-ylazo)phenyl]cyclohexanol (11) was prepared according to general procedure B by quenching the anion derived from [(4-bromophenyl)azo]pyrrolidine (3) with cyclohexanol. This product was unstable to chromatography on silica gel or on standing in the cold and was thus carried over to the reductive cleavage without further purification. The presence of the desired product **11** was noted from the ^{1}H-NMR of the crude material: ^{1}H-NMR ($CDCl_3$) δ 1.20 (2 H, m, CH_2), 1.30 (8 H, m, CH_2), 1.96 (4 H, broad s, CH_2CH_2), 2.72 (4 H, m, CH_2NCH_2), 7.16–7.40 (4 H, m, =CH-).

2-[4-(Pyrrolidin-1-ylazo)phenyl]propan-2-ol (12) was prepared according to general procedure B by quenching the anion derived from [(4-bromophenyl)azo]pyrrolidine (3) with acetone. After workup as described, the crude material was carried over to the reductive cleavage reaction without further purification: ^{1}H-NMR ($CDCl_3$) δ 1.48 (6 H, s, CH_3), 1.92 (4 H, broad s, CH_2CH_2), 3.68 (4 H, broad s, CH_2NCH_2), 7.25 (2 H, d, J = 7, =CH-), 7.33 (2 H, d, J = 7, =CH-).

1-Phenyl-1-[4-(pyrrolidin-1-ylazo)phenyl]ethanol (13) was prepared according to general procedure B by quenching the anion derived from [(4-bromophenyl)azo]pyrrolidine (3) with acetophenone. After workup as described, the crude product was carried over to the reductive cleavage reaction without further purification: ^{1}H-NMR ($CDCl_3$) δ 1.92 (3 H, s, CH_3), 1.98 (4 H, broad s, CH_2CH_2), 3.74 (4 H, broad s, CH_2NCH_2), 7.14–7.38 (7 H, m, =CH-), 7.31 (2 H, s, =CH-).

[4-(Tributylstannyl)phenyl]-2-(pyrrolidin-1-yl)diazene (14) was prepared according to general procedure B by quenching the anion derived from [(4-bromophenyl)azo]pyrrolidine (3) with tributyltin chloride. The product was chromatographed on silica gel with 5:1 hexane/EtOAc to give **14** as an oil in 58% yield: ^{1}H-NMR ($CDCl_3$) δ 0.81 (9 H, t, J = 7, CH_3), 0.96 (6 H, m, CH_2), 1.24 (6 H, m, CH_2), 1.45 (6 H, m, CH_2), 1.95 (4 H, broad s, CH_2CH_2), 3.72 (4 H, broad s, CH_2NCH_2), 7.28 (2 H, d, J = 7, =CH-), 7.34 (2 H, d, J = 7, =CH-); MS M^+ = 465; $(M - C_4H_9)^+$ = 408; high resolution mass spectrum calcd 465.2166, found 465.2158.

General Procedure C for the Reductive Cleavage of Triazene Derivatives to the Anilines. 4-(Trimethylsilyl)-aniline (24). A solution of 1.11 g of [[4-(trimethylsilyl)phenyl]-azo]pyrrolidine (**15**) in 150 mL of methanol and 150 mL of 1 M KOH was treated at room temperature with 10 g of aluminum–nickel alloy[24] added portionwise over 25 min. During this

(24) Aldrich Chemical Co., Inc., Aluminum–nickel catalyst, Al–Ni 50/50 powder (Catalog No. 22,165-1) was used.

addition, the temperature of the reaction mixture was maintained below 30 °C with an ice/water bath. After warming to room temperature and stirring for 18 h, the solids were separated by filtration and the residual methanol was removed on the rotary evaporator. The residues were extracted with ether and the extracts were dried with $MgSO_4$. Addition of a solution of HCl gas in ether to the filtrate gave the crystalline HCl salt in 38% yield: mp 110–111 °C (gas evolved); ^{1}H-NMR (DMSO-d_6) δ 0.27 (9 H, s, $Si(CH_3)_3$), 7.36 (2 H, d, J = 7, =CH-), 7.62 (2 H, d, J = 7, =CH-); MS (free base) M^+ = 165; $(M - CH_3)^+$ = 150. Anal. Calcd for $C_9H_{15}NSi$·HCl (201.77): C, 53.57; H, 7.99; N, 6.94. Found: C, 53.26; H, 7.92; N, 6.66.

2-Aminobenzoic acid (16) was prepared according to general procedure C except that the aqueous quench was adjusted to pH 4.8 with concd HCl and the product was isolated by extraction with ether and crystallization upon concentration to give **16** in 37% yield: mp 143–145 °C, undepressed on admixture with an authentic sample. ^{1}H-NMR ($CDCl_3$) δ 6.45–6.68 (2 H, m, =CH-), 7.28 (1 H, t, J = 7, =CH-), 7.91 (1 H, d, J = 7, =CH-).

1-(2-Aminophenyl)-1-phenylethanol (17) was prepared according to general procedure C as an oil in 88% yield after chromatography on silica gel using 4:1 hexane/EtOAc as eluent and was converted to its crystalline HCl salt in ether: mp 124–125 °C; ^{1}H-NMR (free base, $CDCl_3$) δ 1.82 (3 H, s, CH_3), 3.70 (2 H, broad s, NH_2), 6.58 (1 H, d, J = 7, =CH-), 6.80 (1 H, t, J = 7, =CH-), 6.98–7.42 (7 H, m, =CH-); MS M^+ = 213; (M – OH, $NH_2)^+$ = 180. Anal. Calcd for $C_{14}H_{15}NO$·HCl (249.74): C, 67.33; H, 6.46; N, 5.61. Found: C, 67.17; H, 6.18; N, 5.47.

3-Deuteroaniline (18) was prepared from compound **8** according to general procedure C except that the methanol was evaporated from the filtrate remaining from removal of the Ni/Al alloy residues and the aniline was isolated by steam distillation, addition of HCl to the distillate, and evaporation to dryness on the rotary evaporator to give 3-deuteroaniline hydrochloride in 55% yield: mp 196–198 °C, undepressed on admixture with authentic aniline hydrochloride: MS M^+ = 94; $(M - NH_2)^+$ = 78.

2-(3-Aminophenyl)propan-2-ol (19) was prepared according to general procedure C in 68% yield: mp = 42.0–45.5 °C (CH_3-CN/ether); ^{1}H-NMR ($CDCl_3$) δ 1.56 (6 H, s, CH_3), 3.66 (3 H, broad s, OH, NH_2), 6.56 (1 H, d, J = 7, =CH-), 6.83 (1 H, d, J = 7, =CH-), 6.84 (1 H, s, =CH-), 7.12 (1 H, t, J = 7, =CH-); MS M^+ = 151. Anal. Calcd for $C_9H_{13}NO$ (151.20): C, 71.48; H, 8.68; N, 9.26. Found: C, 71.20; H, 8.63; N, 8.98.

(4-Aminophenyl)benzo[1,3]dioxol-5-ylmethanol (20) was prepared according to general procedure C in 42% yield: mp 103–104 °C (ether); ^{1}H-NMR ($CDCl_3$) δ 3.58 (2 H, broad s, NH_2), 5.60 (1 H, s, CH), 5.86 (2 H, s, OCH_2O), 6.58 (2 H, d, J = 7, =CH-), 6.68 (1 H, d, J = 7, =CH-), 6.78 (1 H, d, J = 7, =CH-), 6.80 (1 H, s, =CH-), 7.07 (2 H, d, J = 7, =CH-). MS M^+ = 243; $(M - OH)^+$ = 226. Anal. Calcd for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.02; H, 5.31; N, 5.82.

1-(4-Aminophenyl)cyclohexanol (21) was prepared according to general procedure C in 45% yield after chromatography on silica gel using EtOAc as eluent: mp 91–93 °C (hexane/ether); ^{1}H-NMR ($CDCl_3$) δ 1.08 (2 H, m, CH_2), 1.30–1.70 (8 H, m, CH_2), 3.54 (3 H, broad s, NH_2, OH), 6.59 (2 H, d, J = 7, =CH-), 7.23 (2 H, d, J = 7, =CH-); MS M^+ = 191; $(M - H_2O)^+$ = 173; $(M - C_3H_7)^+$ = 148. Anal. Calcd for $C_{12}H_{17}NO$ (191.27): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.32; H, 9.24; N, 7.42.

2-(4-Aminophenyl)propan-2-ol (22) was prepared according to general procedure C as an oil in 48% yield after chromatography on silica gel using 4:1 hexane/EtOAc as eluent: ^{1}H-NMR ($CDCl_3$) δ 1.46 (6 H, s, CH_3), 3.54 (3 H, broad s, NH_2, OH), 6.57 (2 H, d, J = 7, =CH-), 7.20 (2 H, d, J = 7, =CH-); MS M^+ = 151; $(M - H_2O)^+$ = 133; $(M - NH_2, OH)^+$ = 118; high resolution mass spectrum calcd 151.0997, found 151.0976.

1-(4-Aminophenyl)-1-phenylethanol (23) was prepared according to general procedure C in 49% yield after chromatography on silica gel using 5:1 hexane/EtOAc as eluent: mp 60.5–62.5 °C (hexane/EtOAc); ^{1}H-NMR ($CDCl_3$) δ 1.88 (3 H, s, CH_3), 6.58 (2 H, d, J = 7, =CH-), 7.14 (2 H, d, J = 7, =CH-), 7.16–7.38 (5 H, m, =CH-); MS M^+ = 213; $(M - CH_3)^+$ = 198; $(M - H_2O)^+$ = 195; $(M - NH_2, OH)^+$ = 180. Anal. Calcd for $C_{14}H_{15}NO$ (213.27): C, 78.84; H, 7.09; N, 6.57. Found: C, 78.57; H, 6.99; N, 6.44.

***m*-Xylene (29) from [(3,5-Dimethylphenyl)azo]pyrrolidine.** [(3,5-Dimethylphenyl)azo]pyrrolidine (**25**) (4.00 g, 19.7 mmol) was added to 58 mL of 30% H_3PO_2 at 5 °C and then 10.35 g of Cu_2O was added slowly in portionwise manner to the mixture. A slightly exothermic reaction occurred, the temperature being maintained close to 5 °C with an ice bath. After 1 h at 0–5 °C, the reaction mixture was allowed to warm to room temperature and stir overnight. The copper salts were then filtered and the filtrate was extracted with ether. The ethereal extracts were washed with 10% NaOH and then dried with brine and $MgSO_4$. The product solution was concentrated and distilled to give 28% of *m*-xylene, identical with an authentic sample by 300-MHz ^{1}H-NMR.

In like fashion, **benzene (34)** was prepared from (phenylazo)-pyrrolidine in 65% yield (headspace analysis).

Mesitylene (30) from [(3,5-dimethylphenyl)azo]pyrrolidine. [(3,5-Dimethylphenyl)azo]pyrrolidine (**25**) (1.16 g, 5.7 mmol) and tetramethyltin (1.22 g, 6.84 mmol) were combined in 23 mL of acetonitrile in a flame-dried 200-mL three-necked flask. Then 128 mg (0.57 mmol) of palladium(II) acetate was added followed by 1.04 mL of 48% HBF_4. A slight warming of the solution and gas evolution was noted. After 1 h, TLC (4:1 hexane/EtOAc) showed that none of the triazene remained. The solids were separated by filtration and the filtrate was partitioned between ether and water. The ethereal extracts were washed with 10% NaOH solution and brine and dried with $MgSO_4$, and the solvent was evaporated to give a residue which was distilled, yielding 0.6 g (25%) of mesitylene (**30**) bp 60 °C/23 mm, identical to an authentic sample (300-MHz ^{1}H-NMR).

In like fashion, **toluene (35)** was prepared from (phenylazo)-pyrrolidine in 72% yield (headspace analysis).

Benzonitrile (33) from (Phenylazo)pyrrolidine. (Phenylazo)pyrrolidine (**26**) (0.86 g, 4.9 mmol) was added to a cold (5 °C) suspension of 1.21 g (24.6 mmol) of NaCN and 2.2 g (24.6 mmol) of CuCN in 10 mL of water and 5 mL of toluene. The pH was adjusted to 1 with 15 mL of 10% HCl and then 20 mL of additional water was added. After 1 h in the cold, the reaction mixture was brought to room temperature and stirred for 2.5 h. The solids were filtered and the filtrate was extracted with ether. The ethereal extracts were dried with brine and $MgSO_4$ and evaporated. A yield of 72% of benzonitrile (**33**) was determined by headspace analysis of the residues.