Table II. Percentage of 3 and 4 as a Function of Time of Photolysis[a]

time, h	%3	%4	fragmentation ratio[b]
0	100.0	0.0	
12	36.3	18.1	0.28
14	31.9	19.4	0.28
16	32.6	21.2	0.31
18	27.8	20.3	0.25
20	25.7	22.6	0.30
22	22.4	23.8	0.31
24	21.3	24.1	0.30

[a] Adamantane was used as the standard; the area of peak for 4 was corrected by a calibration factor of 1.05. [b] Percent 4 formed/percent 3 consumed.

2 (190 °C), and 3 (89 °C)] showed the presence of **4**, **5**,[7] and **6**[14] which were characterized by their identity with authentic specimens with regard to ^{1}H NMR and IR spectra and retention volumes on each of the three GLC columns indicated.

The photolysis was repeated, and 2-mL aliquots were removed after appropriate periods of time; analysis of them by GLC [column 1 (90 °C)] gave the data of Table I.

Photolysis of Cyclohexene. Irradiation at 10 °C of neat cyclohexene (5 mL), contained in a quartz ampule, for 25 h followed by GLC analysis [column 1 (139 °C)] showed formation of **6** and the same unidentified component as was produced by photolysis of **3**.

Registry No. **3**, 56666-90-1; **4**, 931-88-4; **5**, 53282-47-6; **6**, 1541-20-4.

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Convenient Synthesis of Aryl Halides from Arylamines via Treatment of 1-Aryl-3,3-dialkyltriazenes with Trimethylsilyl Halides

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In recent years, the preparation of haloarenes from anilines or other arenes has departed radically from the early approach of Sandmeyer,[2] and halogenation methods involving metalation,[3] in situ diazotization,[4] halogen abstraction,[4-8] and substitutive deamination[9] have all been developed. The involvement of aryl cations in diazonium salt decomposition reactions has been the subject of considerable controversy.[10] The understanding of the dediazoniation process is complicated by the fact that its mechanism is not unique but is quite dependent on the reaction conditions. Dediazoniation can occur by both ionic and free-radical paths.[11]

Previous syntheses of aryl halides from arylamines have involved initial diazotization of arylamines followed by decomposition of the diazonium salt in the presence of a halide ion or a halogen radical source.[4,8,9] Although satisfactory yields of aryl halides are usually obtained, these reactions are complicated by numerous competing reactions (Scheme I). Recently, numerous attempts have been made to gain control of side reactions. For example, decomposition of diazonium salts in nonpolar organic media has been conclusively demonstrated to generate aryl radicals,[12] and satisfactory yields of aryl halides could be obtained by using polyhalogenomethanes as a halogen source.[8] However, aryl radicals abstract halogen from polyhalogenomethanes with variable efficiency,[4,7,13] which limits the synthetic importance of the reaction. The recent successful uses of trimethylsilyl bromide and trimethylsilyl iodide as, inter alia, ether, ester, and 1,3-dioxolane cleavage reagents[14] prompted us to investigate the decomposition

Scheme I

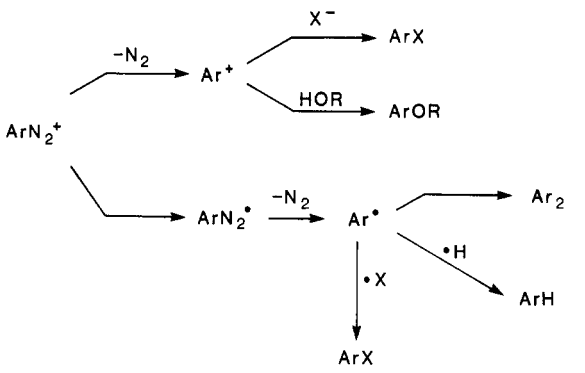

Table I. Aryl Halide Yields

compd	chemical yield,[a] %	compd	chemical yield,[a] %
3a	65[b] (70)	3e	60[c]
3b	75[b] (80)	3f	72[c]
3c	92[b] (76)	3g	80[c]
3d	83[b] (82)	3h	95[c]

[a] All compounds were fully characterized by standard spectral methods. [b] Chemical yields reported are for isolated, chromatographically pure substances. Radiochemical yields of aromatic radioiodides ($Ar^{125}I$ and/or $Ar^{131}I$) are indicated in parentheses and refer to the conversion free radioiodide ⟶ aromatic radioiodide. Radiochemical purities were >99%. [c] Yields measured by HPLC.

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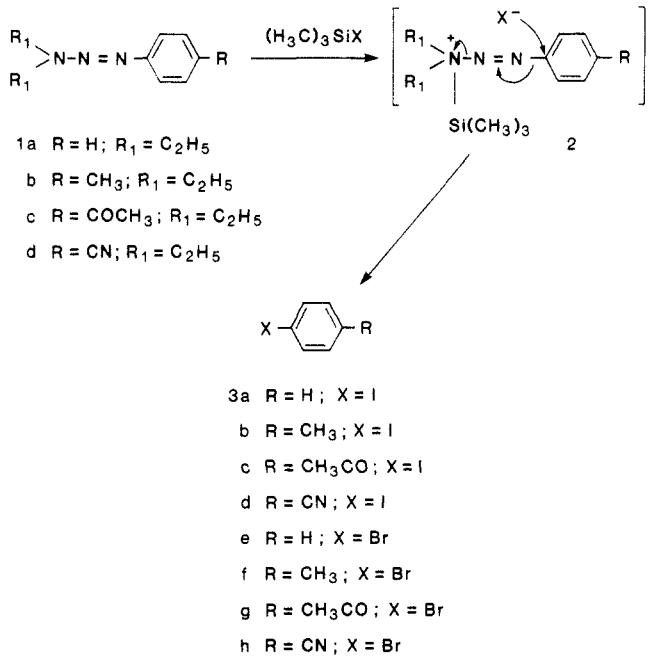
Scheme II



reaction of 1-aryl-3,3-diethyltriazenes (1) in the presence of those reagents. Treatment of 1-aryl-3,3-diethyltriazenes with trimethylsilyl halides in acetonitrile at 60 °C resulted in the rapid and quantitative evolution of nitrogen and in the formation of aryl halides (Table I). 1-Aryl-3,3-diethyltriazenes were prepared by a conventional route in high yield,[15] and trimethylsilyl iodide and bromide were produced in situ[16] by the reaction of trimethylsilyl chloride with sodium iodide or lithium bromide, respectively. The high reactivity of trimethylsilyl halides toward 1-aryl-3,3-dialkyltriazenes may be explained in terms of their strong electrophilicity and the marked affinity of the trimethylsilyl group toward nitrogen. The present reaction pathway may involve formation of **2** by initial attack of the nitrogen lone pair by the trimethylsilyl halide. Compound **2**, upon nucleophilic attack by halide ions, furnishes the aryl halide **3** (Scheme II). The reaction rate seemed to be markedly dependent on the nature of the free halide ion in solution; iodide ion reacted faster than bromide ion, and chloride ion was only converted to the aryl chloride after an extended reaction period. In addition, in the absence of trimethylsilyl chloride, neither iodide not bromide ion reacted with the aryldialkyltriazenes under our experimental conditions.

The reaction of aromatic dialkyltriazenes with trimethylsilyl halides herein reported suggests that this type of reaction is a synthetically useful method for conversion of arylamines to aryl halides. In addition, it is sufficiently mild to permit selection of experimental conditions that would leave intact in many instances normally sensitive groups[14,16,17] (R in structure 1, Scheme II). Furthermore, since the trimethylsilyl iodide and bromide can be prepared in situ by the reaction of trimethylsilyl chloride with sodium iodide or lithium bromide, this method is applicable to the preparation of aromatic radiohalide compounds. For example aromatic radiohalide derivatives may be prepared from bromide (^{75}Br or ^{77}Br) and iodide (^{123}I, ^{125}I, or ^{131}I) with high radiochemical purity and yields (Table I) which makes this synthetic method useful for the preparation of radiopharmaceuticals of medicinal interest. Such applications are currently underway in our laboratories.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The IR spectra were determined on a Perkin-Elmer infrared spectrophotometer, Model 710B. Chemical shifts are expressed as part per million (δ) from internal tetramethylsilane. High-pressure liquid chromatography (HPLC) was carried out on a Beckman Model 334 instrument (Ultrasphere ODS column, 5 μm, 4.6 × 150 mm, 25% 100-mM potassium phosphate (pH 7.4) and 75% MeOH, flow rate 1.0 mL/min; ultraviolet detector). Coupling of a radioactivity detector to the system permitted simultaneous analysis of radiochemical purity (Table I). Unless stated otherwise, all reagents and chemicals were obtained commercially and were used without further purification. The commercially obtained iodide (^{125}I or ^{131}I) in 0.1 N NaOH solution (New England Nuclear) was extracted with freshly distilled 2-butanone (4 × 3 mL) and dried ($CaSO_4$), and the solvent was evaporated under reduced pressure, affording the anhydrous sodium iodide-^{125}I or -^{131}I.

Aromatic Dialkyltriazenes 1.[15] To a solution containing 0.1 mol of arylamine in a mixture of 25 mL of concentrated HCl and 25 mL of water was added dropwise a solution of 7.5 g (0.108 mol) of sodium nitrite in 25 mL of water at 0 °C. The reaction mixture was stirred at 0 °C for an additional 30 min and was then transferred to a solution containing 20.7 g (0.15 mol) of K_2CO_3 and 11.0 g of diethylamine in 200 mL of ice–water. The reaction mixture was then taken up in ether, and the etheral extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the diethyltriazenes 1.

3,3-Diethyl-1-phenyl-1-triazene (1a): yield 92%; bp 36–37 °C (0.04 mmHg) [lit.[18] bp 95–96 °C (6 mmHg)]; IR (neat) 2960, 2920, 2850, 1580, 1460, 1410, 1380, 1340, 1240, 1200, 1140, 1100, 1060, 760 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (t, 6 H, J = 7 Hz), 3.75 (q, 4 H, J = 7 Hz), 7.00–7.55 (m, 5 H).

3,3-Diethyl-1-(4-methylphenyl)-1-triazene (1b): yield 90%; bp 98–100 °C (0.04 mmHg) [lit.[19] 110–111 °C (0.1 mmHg)]; IR (neat) 2970, 2930, 2850, 1500, 1450, 1430, 1400, 1340, 1230, 1200, 1100, 820 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, 6 H, J = 7 Hz), 2.32 (s 3 H), 3.70 (q, 4 H, J = 7 Hz), 7.12 (d, 2 H, J = 8.5 Hz), 7.75 (d, 2 H, J = 8.5 Hz).

1-(*p*-Acetophenyl)-3,3-diethyl-1-triazene (1c):[20] yield 88%; IR (neat) 2980, 2940, 2850, 1680, 1600, 1570, 1460, 1430, 1400, 1340, 1270, 1240, 1200, 1160, 1110, 960, 850, 770, 720 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz), 2.52 (s, 3 H), 3.80 (q, 4 H, J = 7 Hz), 7.43 (d, 2 H, J = 8.5 Hz), 7.92 (d, 2 H, J = 8.5 Hz).

1-(4-Cyanophenyl)-3,3-diethyl-1-triazene (1d). Recrystallization from methanol gave a yellow crystalline solid: mp 38–39 °C; yield 90%; IR (CCl_4) 2980, 2930, 2860, 2240, 1600, 1490, 1460, 1430, 1400, 1330, 1240, 1200, 1160, 1110, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7 Hz), 3.80 (q, 4 H, J = 7 Hz), 7.43 (d, 2 H, J = 9 Hz), 7.62 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.37; H, 6.96; N, 27.83.

Aryl Halide Preparation. General Procedure. To a solution containing 1.0 mmol of the diethyltriazene and 2.0 mmol NaI (or LiBr)[21] in 10 mL of acetonitrile was added 163 mg (1.5 mmol) of trimethylsilyl chloride. The mixture was stirred at 60 °C for 5 min for the iodide and up to 20 min for the bromide. The progress of the reaction was monitored by HPLC. After the reaction mixture cooled to room temperature, 30 mL of 5% sodium bicarbonate solution was added. The mixture was extracted with

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(21) For preparation of aromatic radioiodide compounds the amount of NaI was reduced to 1.0 mmol, and 20–40 μCi anhydrous sodium ^{125}I or ^{131}I iodide was added. If high specific activity product was desired, the addition of "cold" free iodide was omitted.

ether (3 × 50 mL). The ether layers were combined, washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude residue was chromatographed on a silica gel column with a 5% pentane–ether mixture as the eluant to give pure aryl halide.[22]

(22) All the aryl halides obtained were identical in every detail with authentic samples.

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Registry No. 1a, 13056-98-9; **1b**, 36719-51-4; **1c**, 52416-22-5; **1d**, 79664-67-8; **3a**, 591-50-4; **3b**, 624-31-7; **3c**, 13329-40-3; **3d**, 3058-39-7; **3e**, 108-86-1; **3f**, 106-38-7; **3g**, 99-90-1; **3h**, 623-00-7; trimethylsilyl iodide, 16029-98-4; trimethylsilyl bromide, 2857-97-8.

Communications

Synthesis of an Aspartame Precursor by Immobilized Thermolysin in an Organic Solvent

Summary: The synthesis of *N*-(benzyloxycarbonyl)-L-aspartyl-L-phenylalanine methyl ester, the precursor of the synthetic sweetener aspartame, from *N*-(benzyloxycarbonyl)-L-aspartic acid and L-phenylalanine methyl ester was carried out in an apparent single phase of the organic solvent by using thermolysin immobilized with various methods.

Sir: Proteinase-catalyzed syntheses of peptides have been drawing increasing attention,[1] and in many cases the synthesis is based on the deposition of a product,[2] which causes the shift of the equilibrium toward a less favorable product.[3] From the practical point of view the use of an immobilized enzyme is of great value,[4] but it is rather impractical in the enzymatic peptide syntheses because of the problem of the separation of an immobilized enzyme from a deposition product. Recently Kuhl et al. have shown that an immobilized enzyme could be applied to the peptide synthesis by employing biphasic water–organic systems.[5] However, this approach is still unsatisfactory, since we found that the column operation, one big attraction with an immobilized enzyme system, is difficult due to the channeling of the two layers in a packed bed of an immobilized enzyme. We extended our research[6] on the enzymatic synthesis of the dipeptide sweetner aspartame[7] and report the new approach to the synthesis of *N*-(benzyloxycarbonyl)-L-aspartyl-L-phenylalanine methyl ester, the precursor of the sweetener, by using immobilized thermolysin in an apparent single phase of an organic solvent.

Table I. Reaction of *N*-(Benzyloxycarbonyl)-L-aspartic Acid with L-Phenylalanine Methyl Ester by Immobilized Thermolysin in Ethyl Acetate[a]

supporting matl for immobilization[b]	reaction time, h	% yield
Amberlite XAD-7	10	85
Amberlite XAD-8	10	93
Amberlite IRA-94	24	61
Toyopearl EAGA	24	83
glass beads CPG-10	24	55
glass beads CPG-10[c]	24	48

[a] Reaction conditions are given in footnote 10. [b] The preparations of these materials are given in footnotes 8 and 9. [c] The second run used immobilized thermolysin recovered from the first run.

Immobilized enzymes were prepared by using crude thermolysin as follows: (1) physical adsorption to Amberlyte XAD-7 and XAD-8;[8] (2) ionic bonding to the anionic ion-exchange resin Amberlite IRA-94;[8] (3) the enzyme was supported by porous glass beads as an aqueous solution without any special interaction between the enzyme and the supporting material;[8] (4) covalent bonding to the ethylenediamine-derivatized hydrophilic polymer gel Toyopearl through glutaraldehyde (this gel is designated as Toyopearl EAGA in Table I).[9] The aqueous suspension of the immobilized enzyme obtained as above was filtered, washed with 0.5% aqueous calcium acetate solution (pH 7.5), and used as the water-wet material for the synthesis of the dipeptide. The reaction between *N*-(benzyloxycarbonyl)-L-aspartic acid with L-phenylalanine methyl ester was carried out by incubating the mixture of the substrates and the water-wet immobilized enzyme in ethyl acetate at 40 °C.[10]

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(8) Immobilization of the enzyme by physical adsorption onto Amberlite XAD-7 and XAD-8, by ionic bonding to Amberlite IRA-94 (all are from Rohm & Haas Co., Ltd.), and by being supported on glass beads (CPG-10, from Electro-Nucleonics, Inc.) were carried out by stirring 10 g of each of the above water-wet supporting materials in 50 mL of 0.5% aqueous calcium acetate solution (pH 7.5) containing 3 g of crude thermolysin (Thermoase, purchased from Daiwa Kasei Co., Ltd., Osaka, Japan, activity 1.6 × 10^6 PU/g) for 3 h. The immobilized enzyme was collected by filtration and washed with 20 mL of the calcium buffer.

(9) The covalent bonding to the hydrophilic polymer gel was performed as follows. The ethylenediamine-derivatized hydrophilic polymer gel (10 g, Toyopearl, commercially available as the column packing material for gel-permeation chromatography from Toyo Soda Manufacturing Co., Ltd.) was stirred in 20 mL of distilled water containing 3 mL of 25% glutaraldehyde at room temperature for 2 h. The activated gel was collected by filtration, washed with water, and then reacted with the enzyme in 50 mL of the calcium buffer containing 3 g of crude thermolysin.

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