and MS with that obtained by the method described above. Because of the observed instability[5,15] of mercaptans **5a,b,** the crude products were generally used without any chromatographic purification.

Disulfide Analogue of Prostaglandin H_2 Methyl Ester (6). To a stirred solution of 130 mg (0.32 mmol) of **5b** in 10 mL of methanol at room temperature was added 38 mg (0.70 mmol) of sodium methoxide, and then O_2 was bubbled through the resulting suspension.[15] After 1 h, the reaction mixture was diluted with 50 mL of H_2O and neutralized with 0.1 N HCl. The methanol was evaporated under reduced pressure, and the product was isolated with methylene chloride to afford 112 mg (87%) of nearly pure **6,** which was further purified by filtration column chromatography on silicic acid silicar CC-7. Elution with ethyl acetate–hexane, 1:3, gave fractions homogeneous by TLC (system A IX)[9b] affording 51 mg of **6** as a pale yellow oil:[3] $[\alpha]_D$ +8.81°; CD (*c* 1; CH_3OH); $[\theta]_{375}$ +1180; $[\theta]_{330}$ 0; $[\theta]_{256}$ +6500; $[\theta]_{242}$ 0; $[\theta]_{234}$ −5580; $[\theta]_{230}$ 0; IR λ_{max} (film) 3450, 1735, 970 cm^{-1}; Raman (neat) 520 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.40 (m, 4 H), 4.00 (m, 1 H), 3.60 (s, 3 H), 0.87 (t, J = 5 Hz, 3 H); mass spectrum *m/e* (electron impact) 398 M^+ (95.34), $M^+ - H_2O$ (6.47), $M^+ - OCH_3$ (13.91), $M^+ - S$ (9.42), $M^+ - SH$ (5.54), $M^+ - (H_2O + OCH_3)$ (7.62), $M^+ - (H_2O + S)$ (13.66), $M^+ - (H_2O + SH)$ (13.60), $M^+ - C_5H_{11}$ (7.02), $M^+ - (OCH_3 + H_2O + SH_2)$ (47.68); mass spectrum (chemical ionization) 455 ($M^+ + C_4H_9$), 437 ($M^+ + C_4H_9 - H_2O$), 399 ($M^+ + 1$), 381 ($M^+ + 1 - H_2O$) base peak, 349 ($M^+ + 1 - H_2O - S$ or CH_3OH). Although the NMR spectrum shows some discrepancies with that of the reported compound[3] (identical IR), the clean chemical ionization mass spectrum (through *m/e* 800) would appear to preclude any alternative dimeric or polymeric structure:[5,15] *m/e* 398.1940, calcd, 398.1949.

Acknowledgment. We wish to thank Dr. Hayashi for kindly exchanging information. A fellowship to A.P. from the C.I.E.S. (Paris) is gratefully acknowledged.

Registry No.—**2a,** 13345-50-1; **2a** methyl ester, 31753-19-2; **2b,** 36323-03-2; **3a,** 67452-66-8; **3b,** 67452-67-9; **3c,** 67452-68-0; **3d,** 67452-42-0; **3e,** 67452-43-1; **3f,** 67452-44-2; **4a,** 67452-45-3; **4b,** 67452-46-4; **5a,** 67452-47-5; **5b,** 61955-20-2; **6,** 61955-22-4; methanesulfonyl chloride, 124-63-0; sodium trithiocarbonate, 534-18-9; 9α,11α-dithiolacetoxy-9,11-dideoxypostaglandin F_2 15-acetate methyl ester, 67452-48-6.

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(7) Zinc borohydride in dimethoxyethane affords predominantly the 9β alcohols in the reduction of 11-deoxypostaglandin E_2 (unpublished results from these laboratories), PGE_2,[5a] and 11-epiprostaglandin E_2[8] derivatives.

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Addition of Cyclic Secondary Amines to Benzo[*b*]thiophene and 3-Methylbenzo[*b*]thiophene

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Metal-catalyzed addition of primary and secondary amines to conjugated hydrocarbons is well documented,[1] and a general method of ethylating amines with ethylene using an alkali metal salt of the amine as catalyst has been described.[2] More recently, Eisenbraun and co-workers have shown that, in addition to reduction products, naphthalene and methylnaphthalenes undergo reductive amination in the presence of sodium and secondary amines.[3] We wish to report the addition of cyclic secondary amines to the C_2–C_3 bond of benzo[*b*]thiophene (**1**) and 3-methylbenzo[*b*]thiophene (**2**) in the presence of an alkali metal salt of the amine. A definite assignment for the position of attachment of nitrogen on C_2 for the adducts can be made using NMR data. 2-Alkylaminobenzo[*b*]thiophenes are readily obtained by aromatization of the adducts.

On stirring (18 h, 40 °C) benzo[*b*]thiophene **1** or **2** in a cyclic secondary amine in the presence of dispersed sodium, an adduct is obtained in high yield (see Table I). Similar addition is performed using an alkali metal salt of the amine instead of dispersed sodium. In this case, the anion of the amine is formed by reaction of the amine with *n*-butyllithium or sodium hydride.

We suggest nucleophilic addition of the anion of the amine as the first step of the reaction. The amine is needed for the protonation of the intermediate carbanion, as supported by the failure of addition of sodamide in toluene or the lithio salt of piperidine in hexane on **1** (Scheme I).

When similar reactions are performed on 2-methylbenzo[*b*]thiophene, 2,3-dimethylbenzo[*b*]thiophene, benzo[*b*]furan, or benzo[*b*]selenophene, no addition has been detected. Heterocycles are recovered unreacted except benzo[*b*]selenophene, which is reduced to ethylbenzene.

When a low molecular weight primary amine, e.g., propylamine,[4] is substituted for a cyclic secondary amine in reac-

Scheme I

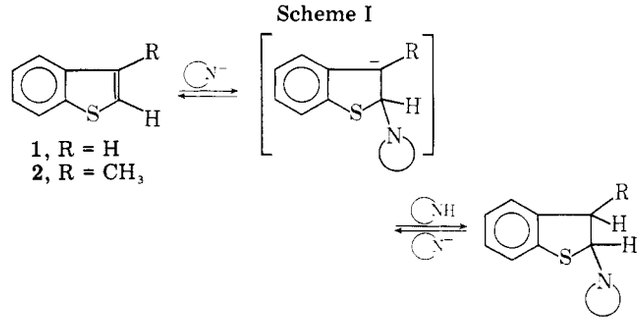

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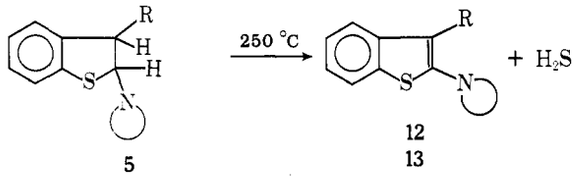
Table I. Addition of Amines to Benzo[*b*]thiophenes

Amine	Registry no.	Benzo[*b*]thiophene recovered, %	Adduct	Registry no.	Yield,[a] %
		Benzo[*b*]thiophene (1)			
Pyrrolidine[b]	123-75-1	10	**3**	66966-29-8	50
Piperidine[b]	110-89-4	12	**4**	41216-62-0	51
Piperidine[c]		21	**4**		46
Morpholine[b]	110-91-8	15	**5**	66902-30-5	45
Morpholine[d]		29	**5**		41
Diethylamine[b]	109-89-7	75	**6**[e]	66902-29-2	5
		3-Methylbenzo[*b*]thiophene (2)			
Pyrrolidine[b]		5	**7**		52
Piperidine[b]		4	**8**		55
Morpholine[b]		12	**9**		42
Propylamine[b,f]	107-10-8	5	**10**[e]	66902-24-7	2
Cyclohexylamine[b,f]	108-91-8	72	**11**[e]	66902-23-6	4

[a] Yield is based on consumed benzo[*b*]thiophene. [b] Reaction in the presence of dispersed sodium. [c] Anion formed by reaction of amine with *n*-butyllithium. [d] Anion formed by reaction of amine with sodium hydride. [e] Characterized only through mass spectra. [f] At room temperature.

Scheme II



5 9 12 13

tion with dispersed sodium, 1 is reduced to ethylbenzene (60%), 2-ethylthiophenol (20%),[5] and *o*-ethylphenyl disulfide (10%), and **2** gives cumene (90%). With cyclohexylamine or an acyclic secondary amine, small amounts of reduction products are formed but yields of adduct are very low.[6]

No reaction with other nucleophilic anions, e.g., an alkali metal salt of thiophenol or alcohols, can be detected.

The NMR data for adducts **7, 8,** and **9** on 3-methylbenzo[*b*]thiophene allow the definite assignment for the position of attachment of the amino group on C_2 and suggest that these adducts are a mixture of trans (major product 95%) and cis isomers.[7]

In each case, on VPC analysis of the crude amino derivatives a small amount of 2-alkylaminobenzo[*b*]thiophene (**12, 13**)[9] can be detected. These products are readily obtained by aromatization of the adducts with stoichiometric amounts of sulfur[10] (Scheme II).

Experimental Section

Benzo[*b*]thiophene was purchased and recrystallized. 3-Methylbenzo[*b*]thiophene was synthesized according to Werner[11] and distilled. All amines were distilled twice from KOH under dry nitrogen.

All melting points are uncorrected. IR spectra were determined using a PE 157G instrument, NMR spectra were recorded on a 60 CHL Jeol spectrometer in $CDCl_3$ using Me_4Si as an internal standard, and mass spectra were determined using a MS 12 spectrometer (University of Bordeaux, France) or a RIBERMAG 10.10. VPC analyses were performed on a F & M 810 GC 6 ft × 0.25 in column packed with 10% SE-30 on Chromosorb W.

Reactions with Dispersed Sodium. General Procedure. To 3.5 g (0.15 g-atom) of dispersed sodium in 60 mL of amine was added a 0.03 M solution of the benzo[*b*]thiophene (**1**, 4 g; **2**, 4.5 g) in 10 mL of amine. The mixture turned red-brown within half an hour and was stirred at 40 °C under dry nitrogen for 18 h. Unreacted sodium generally agglomerated and was removed. The reaction mixture was poured into ice water, acidified with aqueous HCl, and extracted with ether to discard unreacted benzo[*b*]thiophene. The aqueous layer was made basic with KOH and extracted with ether. The adduct-carrying ether layer was dried (Na_2SO_4) and concentrated. The crude adduct was purified by chromatography on alumina and was recrystallized from heptane–toluene when a solid.

2-Pyrrolidino-2,3-dihydrobenzo[*b*]thiophene (3). Reaction of **1** with pyrrolidine: 3.1 g (50%); IR (CCl_4) 3060, 2950, 2870, 2810, 1585, 1460, 1445, 1360, 1120, 1060, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (m, 4 H), 2.4 (m, 4 H), 3.2 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 8 Hz, C_3-H), 3.4 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 2.5 Hz, C_3-H), 5.3 (dd, 1 H, C_2-H), 6.9 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 205 (M^+, 24), 172 (9), 170 (5), 136 (30), 135 (67), 134 (100), 133 (8), 121 (38), 91 (76), 90 (20), 89 (31), 78 (20), 77 (33), 70 (57), 69 (33).

Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82; S, 15.61. Found: C, 70.37; H, 7.42; N, 6.80; S, 15.97.

2-Piperidino-2,3-dihydrobenzo[*b*]thiophene (4). Reaction of **1** with piperidine: 3.35 g (51%); IR (CCl_4) 3060, 2940, 2860, 2805, 1580, 1460, 1445, 1230, 1205, 1120, 1060, 990, 860, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (m, 6 H), 2.35 (m, 4 H), 3.2 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 7.5 Hz, C_3-H), 3.6 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 3 Hz, C_3-H), 5.1 (dd, 1 H, C_2-H), 7 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 48), 186 (8), 137 (8), 136 (31), 135 (48), 134 (30), 96 (38), 91 (23), 85 (15), 84 (100).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.93; H, 7.82; N, 6.18.

2-Morpholino-2,3-dihydrobenzo[*b*]thiophene (5). Reaction of **1** with morpholine: 3 g (45%); mp 75–76 °C; IR (CCl_4) 3060, 2960, 2850, 1580, 1460, 1445, 1120, 1060, 1020, 995, 920 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (m, 4 H), 3.3 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 8 Hz, C_3-H), 3.6 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 2.5 Hz, C_3-H), 3.65 (m, 4 H), 7.1 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 221 (M^+, 67), 188 (4), 136 (32), 135 (100), 134 (75), 121 (8), 98 (32), 91 (37), 86 (30), 77 (12).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; O, 7.23; S, 14.49. Found: C, 64.90; H, 6.91; N, 6.45; O, 7.53; S, 14.31.

2-Pyrrolidino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (7). Reaction of **2** with pyrrolidine: 3.4 g (52%); IR (CCl_4) 3060, 2950, 2860, 2805, 1585, 1460, 1440, 1355, 1250, 1070, 1020, 870, 790, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 3 H, J = 7 Hz, CH_3), 1.7 (m, 4 H), 2.55 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 3 Hz, C_3-H), 5.0 (d, 1 H, C_2-H), 7.0 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 49), 186 (8), 149 (49), 148 (100), 147 (35), 135 (21), 134 (28); 115 (11), 96 (21), 91 (13), 84 (21), 70 (75).

Anal. Calcd for $C_{13}H_{17}NS$: C, 70.93; H, 7.68; N, 6.51; S, 14.87. Found: C, 71.19; H, 7.80; N, 6.38; S, 14.62.

2-Piperidino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (8). Reaction of **2** with piperidine: 3.85 g (55%); IR (CCl_4) 3060, 2930, 2850, 2800, 1580, 1460, 1445, 1230, 1205, 1115, 1105, 1060, 990, 860, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7.5 Hz, CH_3), 1.4 (m, 6 H), 2.35 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 3 Hz, C_3-H), 4.6 (d, 1 H, C_2-H), 7 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 233 (M^+, 45), 150 (22), 149 (66), 148 (100), 147 (22), 135 (22), 134 (22), 110 (20), 96 (20), 85 (25), 84 (78).

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 71.85; H, 8.06; N, 6.21; S, 13.57.

2-Morpholino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (9).

Reaction of **2** with morpholine: 2.85 g (42%); mp 64–65 °C; IR (CCl_4) 3060, 2960, 2850, 1580, 1460, 1440, 1250, 1130, 1115, 1010, 905, 860, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7 Hz, CH_3), 2.45 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 2.5 Hz, C_3-H), 3.6 (m, 4 H), 4.65 (d, 1 H, C_2-H), 7.1 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 235 (M^+, 36), 202 (4), 149 (100), 148 (92), 147 (60), 135 (28), 134 (64), 114 (16), 115 (24), 105 (16), 103 (16), 100 (34), 91 (25), 77 (28).

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95; O, 6.80; S, 13.62. Found: C, 66.35; H, 7.16; N, 6.16; O, 6.99; S, 13.74.

Reaction of Piperidine and Benzo[*b*]thiophene by Means of *n*-Butyllithium. *n*-Butyllithium (0.15 M, 20% solution in hexane) was added to 60 mL of piperidine under nitrogen. The temperature of the mixture was maintained at 40 °C, and a solution of 4 g (0.03 M) of benzo[*b*]thiophene in 10 mL of amine was added. Reaction and isolation were performed as previously described. 2-Piperidino-2,3-dihydrobenzo[*b*]thiophene (**4**) was purified by chromatography, 3 g (46%).

Reaction of Morpholine and Benzo[*b*]thiophene by Means of Sodium Hydride. A mixture of 60 mL of morpholine and 3.6 g (0.15 M) of NaH was refluxed under nitrogen until the evolution of hydrogen ceased and was cooled to 40 °C. The addition of benzo[*b*]-thiophene and the reaction procedure were as previously described. 2-Morpholino-2,3-dihydrobenzo[*b*]thiophene (**5**) was recrystallized from heptane–toluene, 2.7 g (41%).

2-Morpholinobenzo[*b*]thiophene (12). A 1.1-g (0.005 mol) amount of **5** and 0.16 g (0.005 mol) of sulfur were heated at 250 °C until the evolution of H_2S ceased (5 min). The reaction mixture was taken into benzene and decolorized with Norit. Evaporation of benzene and recrystallization from toluene–heptane gave a colorless solid: 0.65 g (60%); mp 179–180 °C; IR (CCl_4) 3060, 2960, 2900, 2855, 2815, 1530, 1440, 1120, 1030, 930, 900, 870, 650 cm^{-1}; NMR (CCl_4) δ 3.2 (m, 4 H), 3.9 (m, 4 H), 6.2 (s, 1 H, C_3-H), 7.3 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 100), 204 (6), 162 (23), 161 (93), 160 (38), 147 (14), 135 (8), 134 (26), 133 (9), 89 (20), 80 (12).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; O, 7.30; S, 14.62. Found: C, 65.71; H, 5.95; N, 6.35; O, 7.55; S, 14.58.

2-Morpholino-3-methylbenzo[*b*]thiophene (13). From aromatization of 100 mg of **9** with 15 mg of sulfur: 65 mg (65%); mp 79–80 °C; IR (CCl_4) 3060, 2960, 2900, 2855, 2820, 1575, 1435, 1190, 1120, 1045, 1015, 980, 880 cm^{-1}; NMR (CCl_4) δ 2.3 (s, 3 H, CH_3), 3.0 (m, 4 H), 3.9 (m, 4 H), 7.4 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 234 (18), 233 (M^+, 100), 232 (27), 218 (5), 188 (5), 176 (11), 175 (50), 174 (58), 173 (16), 161 (12), 160 (30), 159 (10), 147 (30), 134 (11).

Anal. Calcd for $C_{13}H_{15}NOS$: mol wt 233.0874. Found (high-resolution mass spectrum): mol wt 233.0876.

Registry No.—**1**, 95-15-8; **2**, 1455-18-1; *cis*-**7**, 66902-28-1; *trans*-**7**, 66902-27-0; *cis*-**8**, 66902-26-9; *trans*-**8**, 66902-22-5; *cis*-**9**, 66902-21-4; *trans*-**9**, 66902-20-3; **12**, 18774-55-5; **13**, 66902-25-8.

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(6) When the reaction is performed with *n*-butyllithium and a primary amine, no reduction products are formed but the yield of adduct remains disappointingly low.
(7) Cis and trans isomers of adducts **7**, **8**, and **9** cannot be separated, even at an analytical scale. The assumption that the major product is the trans isomer is based on literature data assuming that the chemical shift of H_2 should be higher in the cis isomer than in the trans isomer and that $J_{2,3}$ is higher when H_2 and H_3 are cis than when they are trans.[8]
(8) (a) L. M. Jackman and S. Sternhell, "Application of NMR Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, p 233; (b) J. J. Christol, T. W. Russel, J. R. Mohrig, and D. C. Plorde, *J. Org. Chem.*, **31**, 581 (1966).
(9) The yield is less than 1% based on consumed benzo[*b*]thiophene.
(10) (a) K. R. Brower and E. D. Amstutz, *J. Org. Chem.*, **19**, 411 (1954); (b) B. Iddon and R. M. Scrowston, *Adv. Heterocycl. Chem.*, **11**, 177 (1970).
(11) E. G. G. Werner, *Recl. Trav. Chim. Pays-Bas*, **68**, 509 (1949).

Facile Synthesis of 2-Substituted Imidazoles

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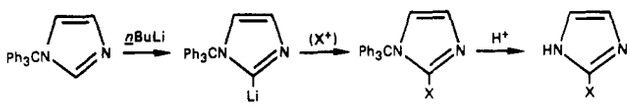
Continuing studies in the biochemistry and pharmacology of ring-fluorinated imidazoles have revealed striking differences in behavior between 2- and 4-fluoro isomers in each series.[1] For example, 2-fluorohistidine displays a wide range of biological activities[2] while 4-fluorohistidine shows little or no activity in the same systems. As part of our efforts to elucidate the causes of these differences, we wished to extend our testing to isomer pairs of the other haloimidazoles—particularly the halohistidines. The 4 (or 5)-halo derivatives can be obtained by direct electrophilic substitution,[3] but no methods are available for preparation of the 2-halo isomers. While 2-fluoro-[4] and 2-chloroimidazoles[5] have been prepared by photochemical decomposition of 2-diazoniumimidazoles, the method fails for bromine or iodine, and there exists no obvious procedure for the introduction of the latter halogens.[6] We have now developed a general synthesis, not only for 2-haloimidazoles, but for a variety of other 2-substituted imidazoles.

In 1-alkyl or 1-arylimidazoles (methyl, benzyl, phenyl), H-2 is the most acidic hydrogen and a carbanion is readily generated at C-2 by reaction with *n*-butyllithium; this carbanion has been used for addition to carbonyl groups[7] as well as to other electrophilic reagents.[8] Unfortunately, the 1-substituent is not easily removed from the product in these cases. *N*-Benzylimidazole can be debenzylated with sodium in liquid ammonia,[9] but bromine or iodine at C-2 undoubtedly would be removed at the same time. We have found that 1-tritylimidazole[10] also forms a carbanion (**1**) with *n*-butyllithium,



1 **2** **3**

that the carbanion reacts readily with various electrophiles to form 1-trityl-2-X-imidazoles (**2**), and that the trityl group is easily removed by mild acid hydrolysis to give 2-X-imidazoles (**3**).

Tables I and II describe compounds prepared by this general method. Yields of **2** are consistently high,[11] except where X is halogen. Attempts to improve yields in the halogenation steps by variation in conditions or source of halogen were unsuccessful. Unreacted tritylimidazole accounted for most of the material loss in these cases. The presence of a single imidazole proton resonance in the NMR spectrum of each **3** supports assignment of the substituent to the 2-position. For **3c**, **3d**, and **3g**, structural assignments were confirmed by comparison with authentic samples. In no case was there formed a detectable quantity of the isomeric 4(5)-X-imidazole, based on NMR and chromatographic evidence.

The preparation of 2-aminoimidazole through the phenyltriazene (**2g**), based on a procedure for the preparation of 1-alkyl-2-aminoimidazoles,[12] has special significance in that it allows a nonreductive introduction of the 2-amino function into a preformed imidazole ring. (In our hands, the catalytic reduction of 2-arylazo-4-X-imidazoles often results in simultaneous loss of the 4-X substituent.[5]) Consistent with the results of others,[12] our attempts to aminate **1** with methoxyamine,[13] *O*-mesitylenesulfonylhydroxylamine,[14] or *O*-2,4-dinitrophenylhydroxylamine[15] were unsuccessful.