Reaction of 4-Bromo-1,2-dimethylbenzene with Various Nucleophiles via Aryne Reaction[1]

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4-Bromo-1,2-dimethylbenzene (**4a**) reacts with a variety of amines, mercaptans, and nitriles under aryne-forming conditions to yield predominantly 4-substituted 1,2-dimethylbenzenes and minor quantities of 3-substituted 1,2-dimethylbenzenes. The product distributions from these reactions are heavily in favor of the 4-substituted isomer since it is formed exclusively from the symmetric 4,5-dimethylbenzyne intermediate (**6**) and partly from the unsymmetric 3,4-dimethylbenzyne intermediate (**5**).

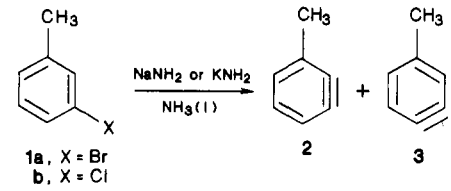
We have shown that disubstituted halobenzenes possessing strong electronegative sustituents generate aryne intermediates that display pronounced regiochemical preferences, yielding good to excellent yields of a single product.[2,3] For example, the reaction of 4-bromoveratrole in the presence of primary amines and potassium amide gives 4-*N*-alkylveratroles in good to excellent yields.

The aryne reaction of 2-bromo-1,4-dimethylbenzene, which contains two weakly directed methyl groups, also yields a single product since the aryne intermediate formed in that reaction is symmetrical.[2] The remaining halodimethylbenzene isomers would be expected give mixtures of aryne products. Of these isomers, we choose to study 4-bromo-1,2-dimethylbenzene on the basis of the following observations reported in the pioneering aryne study by Roberts.[4]

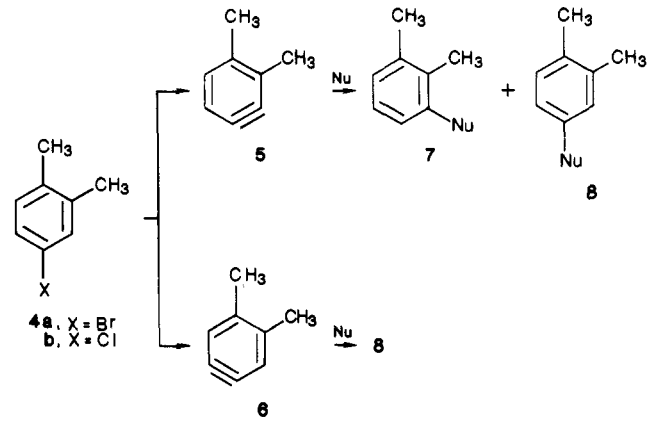
m-Bromo- (**1a**) and *m*-chlorotoluene (**1b**) in the presence of alkali amide in liquid ammonia yield the unsymmetrical 3-methyl- and 4-methylbenzynes (**2** and **3**, respectively). the ratio of these arynes is a function of the halogen atom; **3** is generated from *m*-bromotoluene to a greater extent than **2**, whereas *m*-chlorotoluene preferentially forms **2** over **3**. However, because of the weak inductive effect of the methyl group, neither of these arynes is formed to a much larger extent than the other, which, coupled by the fact that each undergoes amination at both positions of the "triple bond", results in product distriubtions consisting of all three toluidines (see Scheme I). Consequently, the synthetic utilization of the aryne reaction of these halotoluenes has not been explored.

4-Bromo- (**4a**) and 4-chloro-1,2-dimethylbenzene (**4b**) are somewhat similar to *m*-halotoluenes in that two arynes also are expected from these disubstituted haloarenes, namely 3,4-dimethyl- (**5**) and 4,5-dimethylbenzyne (**6**). In addition, the unsymmetrical aryne, **5**, being similar to **2**, would yield both 3-substituted- (**7**) and 4-substituted-1,2-dimethylbenzenes (**8**). However, aryne **6** is symmetrical and would yield only **8**. Further, the 4-bromoarene **4a** should, by analogy to 3-bromotoluene, form aryne **6** in preference to aryne **5** (see Scheme II). Thus, the aryne reaction of **3** would yield only two isomers (as compared to three from halotoluenes) of which the 4-substituted isomer would predominant over the 3-substituted one. Accordingly, the reaction of **4a** with various amines, nitriles, and mercaptans in the presence of alkali amide was conducted and the results reported herein.

Scheme I



Scheme II



Experimental Section

General Aspects. Proton NMR spectra were measured in $CDCl_3$ solutions on a Perkin-Elmer R32 spectrometer at 90 MHz. Infrared spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. Chromatographic analyses and mass spectra (70 eV) were obtained on a Hewlett-Packard Model 5988A gas chromatograph/mass spectrometer equipped with a 12 m × 0.20 mm i.d. capillary column containing cross-linked methyl silicone of 0.33-μm film thickness. Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under a pressure of 1 atm (flash chromatography).[5] All reactions were carried out in flame-dried flasks under a nitrogen atmosphere. Elemental analyses were performed at the microanalytical laboratory of Southern Methodist University.

Starting Materials. The amines, nitriles, mercaptans, 4-chloro-1,2-dimethylbenzene, and 4-amino-1,2-dimethylbenzene were purchased from Aldrich Chemical Co. and were dried and distilled or recrystallized prior to use. 4-Bromo-1,2-dimethylbenzene (**4a**) was prepared by diazotizing 4-amino-1,2-dimethylbenzene in the presence of cuprous bromide and its purity verified by GC/MS.

General Procedure for the Aryne Reactions with Primary and Secondary Amines. Potassium amide (0.05 mol) was prepared from 1.9 g (0.05 mol) of potassium in 50 mL of liquid ammonia containing 0.01 g of ferric nitrate contained in a 250-mL flask equipped with a mechanical stirrer and dry ice condenser.

(1) Supported in part by Grant N-118 from the Welch Foundation, Houston, TX.

(2) Han, Y. X.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397.

(3) Han, Y. X.; Jovanovic, M. V.; Biehl, E. R. *J. Org. Chem.* **1985**, *50*, 1334.

(4) Roberts, J. D.; Vaughan, C. W.; Carlsmith, L. A.; Semenov, D. A. *J. Am. Chem. Soc.* **1956**, *78*, 601, 611.

(5) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2647.

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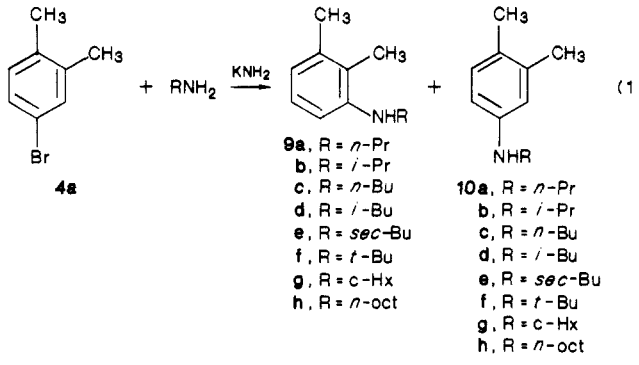
After the discharge of the initial blue solution to gray, which indicated the complete conversion of potassium to potassium amide, the dry ice condenser was replaced with a West condenser, 75 mL of the appropriate amine was added, and the ammonia was evaporated by heating with a steam bath and under a gentle flow of nitrogen. Compound **4a** (4.63 g, 0.025 mol) was added and the mixture refluxed for 30 min. After the mixture was cooled to room temperature, 2.7 g of ammonium chloride and 75 mL of methylene chloride were added and the resulting mixture was stirred vigorously for 10 min and filtered through a medium-sized fritted-glass funnel. The mother liquor was concentrated under vacuum (rotary evaporator) to yield an oil from which a sample (0.1 mg) was subjected to qualitative and quantitative GC/MS analysis. Flash chromatography (95% hexane–5% methylene chloride) of the remaining oil from the reaction of **4** with primary amines and secondary amines yielded the corresponding *N*-alkylxylidines and *N,N*-dialkylxylidines in purities >95%. Analytical samples of the 4-substituted xylidines were obtained by either repeated flash chromatography or vacuum distillation. No attempt was made to purify the minor 3-substituted xylidine products.

General Aryne Reaction with Nitriles and Mercaptans. A solution of sodamide (0.04 mol) in 50 mL of liquid ammonia was prepared in the same manner as described above in the general procedure for aryne reactions with primary and secondary amines. The appropriate nitrile or mercaptan (0.02 mol) was added dropwise, the mixture was stirred for 2 min, and then **4a** (1.85 g, 0.01 mol) was added dropwise. The final solution was stirred for 1 h; then, ammonium chloride (2.1 g, 0.04 mol) was added, and the ammonia was removed by heating with a steam bath. The resulting oil was dissolved in 75 mL of methylene chloride, and the solution was washed with three 50-mL portions of 6 N HCl. The methylene chloride solution was dried (Na_2SO_4) and concentrated under vacuum (rotary evaporator) to yield an oil that consisted of a mixture of nitriles. The identity and amount of each isomer in the mixture were accomplished by GC/MS quantitative and qualitative analysis. The nitriles could not be purified by flash chromatography; however, analytical samples of the 4-substituted 1,2-dimethylbenzenes were obtained by repeated distillation.

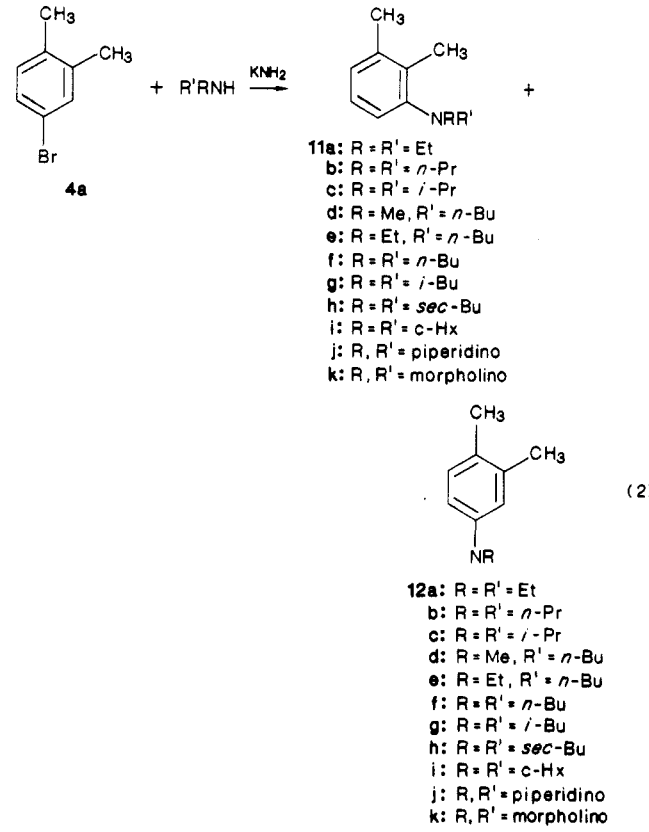
Results and Discussion

The reaction of **4a** and potassium amide with primary amines gave predominantly *N*-alkyl-3,4-xylidines **10** in 71–86% yields plus a small quantity of *N*-alkyl-2,3-xylidine **9** (4–19%) (Table Ia; eq 1). Similarly, the reaction of **4a**



(1)

with secondary amines and potassium amide afforded mainly *N,N*-dialkyl-3,4-xylidines **12** in 72–88% yields and small quantities of *N,N*-dialkyl-2,3-xylidines **11** in yields generally less than 10% (eq 2). The results are listed in Table Ib. The amine product distribution from both reactions was heavily in favor of the 4-substituted product, indicating that aryne **3** is formed preferentially from **4a**. For example, the product distributions of most *N*-alkylxylidines **10** and **9** were about 85:15, respectively, and 90:10 for the *N,N*-dialkylxylidines **12** and **11**, respectively. The higher distributions for the *tert*-butyl- (96:4), diisopropyl- (95:5), diisobutyl- (95:5), and di-*sec*-butylxylidine mixtures (99:1) probably reflect the unfavorable steric interaction

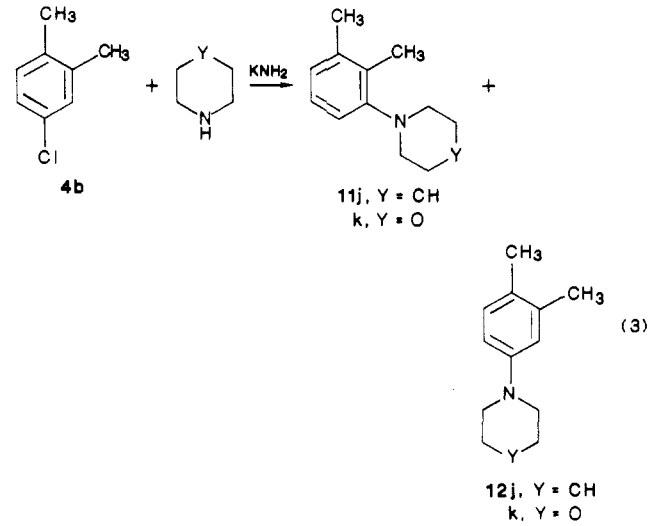


(2)

between the methyl group of aryne **2** and those bulky amines during the formation of the 3-isomer.

The product distributions were obtained by GC/MS qualitative and quantitative analysis of the crude reaction mixtures. Except where noted in Table I, the major products **10** or **12** were obtained in pure state by flash chromatography. These amines were further characterized by NMR and IR spectroscopy (Table 3, supplementary material). The minor amine products **9** or **11**, generally, were not obtained in pure state; however, they were obtained in sufficient purity from the initial flash chromatographic pass of the reaction mixture to allow the assignment of pertinent absorption bands from the NMR and IR spectra of these impure amines.

To ascertain whether the ratio of arynes from **4** was a function of the halogen atom, 4-chloro-*o*-xylene (**4b**) was treated with potassium amide and piperidine. The ratio of 4-piperidyl- and 3-piperidyl-1,2-dimethylbenzenes (**12j**, **11j**; eq 3) produced from **4b** was smaller (75:25) than that



(3)

Table I. Reaction of 4-Bromo-*o*-xylene

a. With Various Alkylamines and Potassium Amide

nucleophile	time, h	overall yield,[a] % 3-isomer (9)	4-isomer (10)	isomer ratio,[b] 9:10	bp,[c] °C/torr
n-propylamine	1	19	76	18:82	73/0.3
isopropylamine	2	15	75	17:83	68–70/0.1
n-butylamine	1	12	78	13:87	76/0.2
isobutylamine	1	12	82	13:87	82–86/0.25
sec-butylamine	2	13	84	13:87	116–118/2.0
tert-butylamine	3	3.6	86	4:96	62/0.2
cyclohexylamine	3	15	71	18:82	156–160/2.0
n-octylamine	2	8.5	85	10:90	176–180/2.0

b. With Dialkylamines and Potassium Amide

nucleophile	time, h	overall yield,[a] % 3-isomer (11)	4-isomer (12)	11:12	bp,[c] °C/torr
diethylamine	2	11	80	12:88	83/0.3
di-*n*-propylamine	2	8.5	77	10:90	86/0.2
diisopropylamine	4	4.0	76	5:95	68–72/0.2
N-methyl-*N*-butylamine	2.5	7.8	79	9:91	116–118/1.0
N-ethyl-*N*-butylamine	3	6.3	84	7:93	125–128/1.0
di-*n*-butylamine	3	12	78	13:87	88–90/0.30
diisobutylamine	3	4.5	86	5:95	90–92/0.35
di-*sec*-butylamine	5	trace	81	1:99	82–84/0.20
dicyclohexylamine	6	7	72	10:90	138–141/0.10
piperidine	3	9	88	10:90	88–90/0.25
morpholine	3.5	9	86	10:90	96–98/0.20

[a] Based on the amount of consumed starting material. [b] Based on the overall yield. [c] Bp range of the major isomer.

Table II. Reaction of 4-Bromo-*o*-xylenes

a. With Various Alkane- and Benzenenitriles in the Presence of Sodium and/or Potassium Amide

nucleophile	time, h	overall yield,[a] % 3-isomer (13)	4-isomer (14)	13:14	bp,[c] °C/torr
acetonitrile	2	15	68	18:82	84/0.2
propionitrile	2	15	67	18:82	87/0.2
butyronitrile	2	13.5	61.5	18:82	92/0.20
valeronitrile	2	14	64	18:82	94–98/0.25
benzyl cyanide	3	16	50	24:76	128/0.20
(3-methoxyphenyl)acetonitrile	3	11.5	65	15:85	*d*
(3,4-dimethoxyphenyl)acetonitrile	3	10.2	58	15:85	*d*
(3,4,5-trimethoxyphenyl)acetonitrile	3	9.2	52	15:85	*d*

b. With Alkyl or Aryl Mercaptans in the Presence of Potassium Amide

nucleophile	time, h	overall yield,[a] % 3-isomer (15)	4-isomer (16)	15:16	bp,[c] °C/torr
ethyl mercaptan	4	17.3	46.7	27:73	72/0.3
isopropyl mercaptan	5	9.2	52	15:85	80–84/0.4
thiophenol	6	8.5	38.5	18:82	130–136/0.5
β-naphthol	8	1	37	3:97	>200/0.4

[a] Based on the amount of consumed starting material. [b] Based on the overall yield. [c] Bp range of the major isomer.

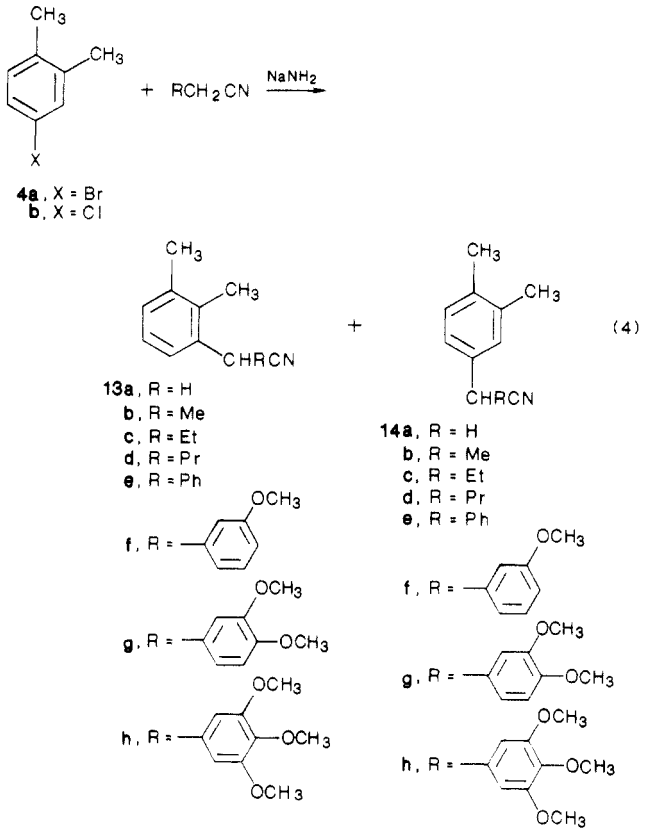
from **4a** (90:10), indicating that the symmetric aryne **3** was formed to a lesser extent from **4b** than from **4a**. The reaction of **4b** with morpholine gave similar results. The influence of the halogen atom on the product distributions in this study is consistent with those observed previously in the aryne reaction of *m*-bromo- and *m*-chlorotoluene.[4]

Thus, the aryne reaction of **4a** provides a convenient method for the synthesis of *N*-alkyl- and *N*,*N*-dialkyl-3,4-xylidines. The synthesis of the former amines is particularly important since several of them serve as important precursors in the synthesis of promising antimetabolic[6] and antiallergetic[7] drugs.

The reaction of **4a** with various anions of nitriles or mercaptans and sodamide in liquid ammonia was carried out to determine the extent to which these anions compete with ammonia for the aryne intermediates **2** and **3**. In all cases, **2** and **3** mainly underwent addition by nitrile anions to form 4- and 3-(cyanoalkyl)-1,2-dimethylbenzenes **14** and **13** in a ratio of 82:18, respectively, and in overall yields of 66–83% (Table IIa; eq 4). The isomer ratios were obtained by GC/MS. These nitrile mixtures could not be purified by flash column chromatography or thick-layer chromatography; however, analytical samples of the 4-(cyanoalkyl)-1,2-xylenes **14** were obtained by repeated distillation of the respective nitrile isomeric reaction mixtures and their structures elucidated further by IR and NMR spectroscopies. We currently are using these mixtures as precursors in the synthesis of various phenethylamine derivatives. Preliminary results indicate that these derivatives derived from **14** can be obtained in pure state by flash chromatography.

The synthetic utility of this reaction is exemplified further by the synthesis of the (methoxyphenyl)-3′,4′-xy-

(6) Warner, P. L.; Bardos, T. J. *J. Med. Chem.* **1970**, *13*, 407.
(7) Buehler, N.; Bosshard, H.; Sallman Ger. Offen. 2804823 (cl. C07D209/36); 17 Aug 1978, Lux. Appl. 76755, 11 Feb 1977: *Chem. Abstr.* **1978**, *89*, 179860*t*.

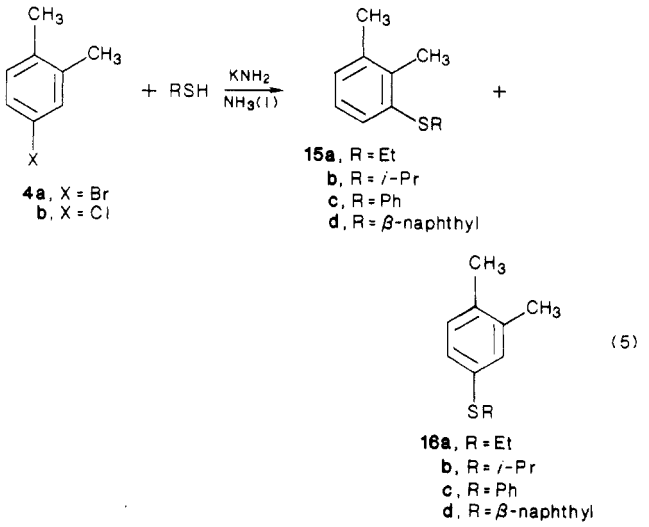


lyl-acetonitriles **13f–h** and **14f–h**. Many naturally occurring active compounds contain one or more methoxyphenyl groups. We currently are testing them for biological activity.

The amount of each aryne from **4a** can be estimated from the product distribution obtained from the acetonitrile reaction in the following way. 3-(Cyanomethyl)-1,2-dimethylbenzene (**13a**) can be formed only by nitrile anion addition to aryne **5**. Further, this addition to the structurally similar 3-toluyne exhibits no regioselectivity; both positions of the aryne undergo addition equally.[8] Thus, the 82:18 isomer ratio from the reaction of **4a** with the anion of acetonitrile indicates that arynes **6** and **5** are formed in a ratio of 64:36, respectively.

Finally, the reaction of **4a** with mercaptides yielded mainly the corresponding 4-mercapto-1,2-dimethylbenzenes **16a–d** in good yields along with minor amounts of the 3-isomer **15–d** (Table II; eq 5). With the exception of 4-(isopropylthio)-1,2-dimethylbenzene (**16b**) the 4-isomers could be obtained in pure state. The spectral data listed in Table IV (supplementary material) are consistent with their proposed structure.

(8) Levine, R.; Biehl, E. R. *J. Org. Chem.* **1975**, *40*, 2416.



We are currently investigating the synthetic aspects of the aryne reactions of other polysubstituted haloaromatic compounds.

Registry No. **4a**, 583-71-1; **9a**, 53164-35-5; **9b**, 63114-76-1; **9c**, 105336-22-9; **9d**, 105336-23-0; **9e**, 105336-25-2; **9f**, 105336-26-3; **9g**, 105336-28-5; **9h**, 105336-29-6; **10a**, 27285-21-8; **10b**, 105336-21-8; **10c**, 27285-22-9; **10d**, 105336-24-1; **10e**, 56038-90-5; **10f**, 105336-27-4; **10g**, 78455-19-3; **10h**, 105336-30-9; **11a**, 3995-36-6; **11b**, 105336-32-1; **11c**, 105336-34-3; **11d**, 105336-36-5; **11e**, 105336-38-7; **11f**, 105336-40-1; **11g**, 105336-42-3; **11i**, 105336-45-6; **11j**, 105336-47-8; **11k**, 105336-49-0; **12a**, 105336-31-0; **12b**, 105336-33-2; **12c**, 105336-35-4; **12d**, 105336-37-6; **12e**, 105336-39-8; **12f**, 105336-41-2; **12g**, 105336-43-4; **12h**, 105336-44-5; **12i**, 105536-46-7; **12j**, 105336-48-9; **12k**, 105336-50-3; **13a**, 76574-43-1; **13b**, 105336-51-4; **13c**, 105336-52-5; **13d**, 105336-54-7; **13e**, 105336-56-9; **13f**, 105336-58-1; **13g**, 105336-60-5; **13h**, 105336-62-7; **14a**, 3020-06-2; **14b**, 105371-71-9; **14c**, 105336-53-6; **14d**, 105336-55-8; **14e**, 105336-57-0; **14f**, 105336-59-2; **14g**, 105336-61-6; **14h**, 105336-63-8; **15a**, 105371-72-0; **15b**, 105336-65-0; **15c**, 105336-67-2; **15d**, 105336-68-3; **16a**, 105336-64-9; **16b**, 105336-66-1; **16c**, 2828-65-1; **16d**, 105336-69-4; propylamine, 107-10-8; isopropylamine, 75-31-0; butylamine, 109-73-9; isobutylamine, 78-81-9; *sec*-butylamine, 13952-84-6; *tert*-butylamine, 75-64-9; cyclohexylamine, 108-91-8; octylamine, 111-86-4; diethylamine, 109-89-7; dipropylamine, 142-84-7; diisopropylamine, 108-18-9; *N*-methyl-*N*-butylamine, 110-68-9; *N*-ethyl-*N*-butylamine, 13360-63-9; dibutylamine, 111-92-2; diisobutylamine, 110-96-3; di-*sec*-butylamine, 626-23-3; dicyclohexylamine, 101-83-7; acetonitrile, 75-05-8; propionitrile, 107-12-0; butyronitrile, 109-74-0; valeronitrile, 110-59-8; benzylcyanide, 140-29-4; (3-methoxyphenyl)acetonitrile, 19924-43-7; (3,4-dimethoxyphenyl)acetonitrile, 93-17-4; (3,4,5-trimethoxyphenyl)acetonitrile, 13338-63-1; ethyl mercaptan, 75-08-1; isopropyl mercaptan, 75-33-2; thiophenol, 108-98-5; β-naphthalenethiol, 91-60-1; piperidine, 110-89-4; morpholine, 110-91-8.

Supplementary Material Available: Listings of elemental analyses and mass spectral, ^{1}H NMR, and IR data (16 pages). Ordering information is given on any current masthead page.