Synthesis of 2-(Alkylamino)benzonitriles from α-(Bromoarylamino)nitriles

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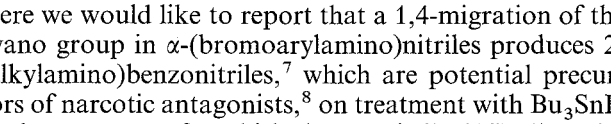
The treatment of α-(bromoarylamino)nitriles with Bu_3SnH/AIBN induced 1,4-cyano group migration which led to 2-(alkylamino)benzonitriles.

A number of intramolecular free radical additions to nitriles have been reported.[1] For example radical intermediates, generated by the deoxygenation of alcohols,[2] or the reduction of ketones,[3] undergo intramolecular ring closure when suitably located cyano groups are present. These reactions provide a new synthesis of cyclopentanones. The synthesis of cyclohexanones has also been accomplished by the addition of radicals to a cyano group.[4] Furthermore, the 1,5-migration of a hydrogen atom[5] and the 1,4-migration of a cyano group[6] have also been observed when δ-cyano radicals are produced.

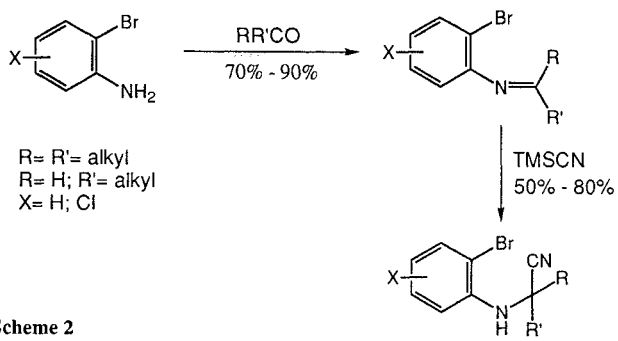
Here we would like to report that a 1,4-migration of the cyano group in α-(bromoarylamino)nitriles produces 2-(alkylamino)benzonitriles,[7] which are potential precursors of narcotic antagonists,[8] on treatment with Bu_3SnH in the presence of azobisisobutyronitrile (AIBN) under reflux (Scheme 1).



R= R'= alkyl
R= H; R'= alkyl
X= H; Cl

Scheme 1

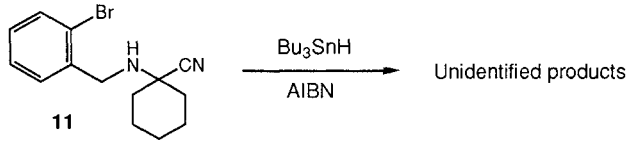
α-(Bromoaryl)aminonitriles **1–5** were prepared from the corresponding 2-bromoaniline. The condensation of the 2-bromoaniline with an aldehyde or a ketone led to the formation of the corresponding imines[9] in good yields (> 70%). Addition of trimethylsilyl cyanide (TMSCN) to the imine generated the corresponding α-(bromoaryl)aminonitrile (Scheme 2).[10] When compounds **1–5** were treated by Bu_3SnH in the presence of AIBN in refluxing toluene the rearranged products **6–10** were obtained with yields superior to 45%. The results are summarized in the Table.



R= R'= alkyl
R= H; R'= alkyl
X= H; Cl

Scheme 2

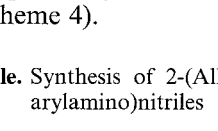
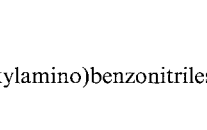
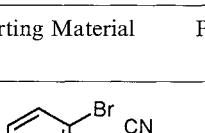
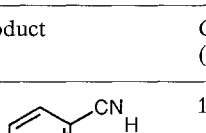
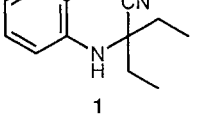
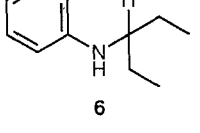
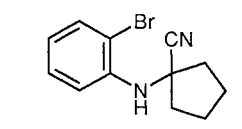
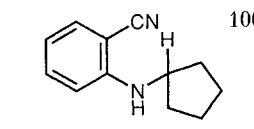
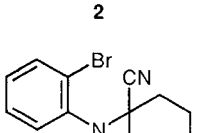
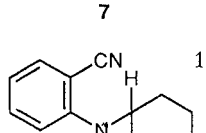
The 1,4-migration of the cyano group is general. The reaction is chemoselective as the chloro substituent was not cleaved. Moreover, a 1,5-migration of the cyano group was not observed when compound **11** was treated with Bu_3SnH/AIBN. Only unidentified products were formed (Scheme 3).

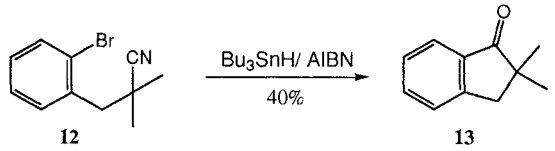


Scheme 3

Furthermore, treatment of 3-(2-bromophenyl)-2,2-dimethylpropionitrile **(12)**, which carries no amino group with Bu_3SnH in the presence of AIBN in refluxing toluene led primarily to the formation of cyclopentanone **13**[11] (Scheme 4).

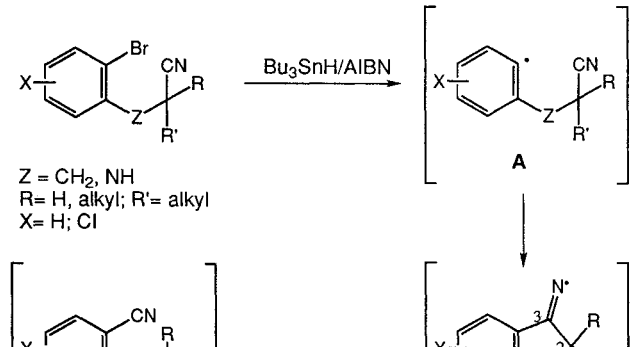
Table. Synthesis of 2-(Alkylamino)benzonitriles from α-(Bromoarylamino)nitriles

Starting Material	Product	Conversion (%)	Yield (%)
 1	 6	100	58
 2	 7	100	65
 3	 8	100	60
 4	 9	50	45
 5	 10	50	45



Scheme 4

The formation of compounds **6–10** and **13** can be explained by the fact that the radical, resulting from the cleavage of the C–Br bond, attacked the cyano group to produce the imine radical **B**. The cleavage of the C_2–C_3 bond is favorable as the α-amino radical (Z = NH) is more stable than the alkyl radical **C** (Z = CH_2) by ca. 16 kcal/mol (Scheme 5).[12]



Scheme 5

With compound **11**, neither the migration of the cyano group nor the formation of the cyclized product was observed. This can be explained by postulating that the attack of the radical at the cyano group cannot occur with a suitable trajectory (angle of 120°)[13] because of the steric interactions between the phenyl and the cyano groups.

In summary, this study has disclosed that 1,4-migration of the cyano group in α-(bromoaryl)aminonitrile compounds is a facile process and leads to 2-(alkylamino)-benzonitriles in good yields.

NMR spectra ($CDCl_3$, TMS) were recorded using a Bruker AC 300 spectrometer. IR spectra were obtained on a Perkin-Elmer 298 IR spectrophotometer instrument. MS were performed at 70 eV and were recorded on a HP 5890/5971 mass selective detector. Merck silica gel (Kieselgel 60 F_{254}) was used for analytical TLC. Column chromatography was performed with Merck silica gel (Kieselgel 60, 230–400 mesh).

All commercially available chemicals and solvents were used as received from the suppliers. Toluene was distilled from CaH_2 and stored under N_2.

2-[(2-Bromophenyl)amino]-2-ethylbutanenitrile (1):
To a stirred solution of pentan-3-one (0.59 mL, 5.8 mmol) and 2-bromoaniline (1 g, 5.8 mmol) in glacial AcOH (10 mL) was added trimethylsilyl cyanide (0.77 mL, 5.8 mmol) dropwise over a period of 20 min, while maintaining the temperature below 40 °C. The solution was stirred for an additional 30 min and then poured into cold NH_4OH solution (10 mL of aq 35% NH_4OH, 10 g of crushed ice). Furthermore, an aq solution of NH_4OH (35%) was slowly added to the mixture until pH 10 was reached. The resulting solution was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography to afford **1** as an oil; yield: 0.55 g (35%); R_f 0.66 (EtOAc/cyclohexane, 10:90).

IR (film): ν = 3460, 2240 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (dd, J = 8.57, 1.70 Hz, 1 H), 7.33–7.28 (m, 2 H), 6.73 (td, J = 8.57, 1.70 Hz, 1 H), 4.51 (s, 1 H), 2.05–1.70 (m, 4 H), 1.00 (t, J = 7.58 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9 (s), 132.7 (d), 128.2 (d), 120.3 (s), 120.0 (d), 114.6 (d), 111.7 (s), 57.0 (s), 29.4 (t, 2C), 7.8 (q, 2C).

MS (EI, 70 eV): m/z = 266 (M^+, 18), 268 (19), 239 (100), 237 (94), 212 (58), 210 (61).

α-(Bromoarylamino)nitriles 2–4; General Procedure:
The crude imine[14] (5.8 mmol), prepared from the corresponding substituted 2-bromoaniline and ketone, was dissolved in EtOH (10 mL). The solution was treated with trimethylsilyl cyanide (1.56 mL, 11.6 mmol). After 48 h reflux, the solution was cooled and concentrated under vacuo. The crude product was purified by flash chromatography.

1-[(2-Bromophenyl)amino]cyclopentane-1-carbonitrile **(2)**; oil; yield: 54%; R_f 0.55 (EtOAc/cyclohexane, 20:80).

IR (film): ν = 3460, 2240 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50 (dd, J = 8.57, 1.70 Hz, 1 H), 7.28 (td, J = 8.57, 1.70 Hz, 1 H), 7.10 (dd, J = 8.57, 1.70 Hz, 1 H), 6.72 (td, J = 8.57, 1.70 Hz, 1 H), 4.53 (br s, 1 H), 2.50–2.29 (m, 2 H), 2.25–2.08 (m, 2 H), 1.90–1.20 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2 (s), 132.7 (d), 128.3 (d), 120.0 (d), 119.0 (s), 114.2 (d), 111.2 (s), 56.9 (s), 39.9 (t, 2C), 23.6 (t, 2C).

MS (EI, 70 eV): m/z = 237 (M^+ – HCN, 54), 239 (52), 208 (100), 210 (96), 157 (16), 155 (15).

1-[(2-Bromophenyl)amino]cyclohexane-1-carbonitrile **(3)**; solid, mp 98–99 °C; yield: 43%; R_f 0.50 (EtOAc/cyclohexane, 15:85).

IR (film): ν = 3460, 2240 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (dd, J = 7.35, 1.47 Hz, 1 H), 7.28–7.18 (m, 2 H), 6.60 (td, J = 7.35, 1.47 Hz, 1 H), 4.35 (br s, 1 H), 2.45–2.29 (m, 2 H), 1.85–1.55 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7 (s), 132.7 (d), 128.2 (d), 120.2 (d), 119.2 (s), 115.2 (d), 111.9 (s), 53.3 (s), 36.0 (t, 2C), 24.6 (t), 21.8 (t, 2C).

MS (EI, 70 eV): m/z = 251 (M^+ – HCN, 51), 253 (51), 208 (100), 210 (96), 155 (25), 157 (25).

1-[(2-Bromo-4-chlorophenyl)amino]cyclohexane-1-carbonitrile **(4)**; solid, mp 100–101 °C; yield: 70%; R_f 0.55 (EtOAc/cyclohexane, 15:85).

IR (film): ν = 3450, 2240 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, J = 0.74 Hz, 1 H), 7.03 (dd, J = 9.00, 0.74 Hz, 1 H), 6.94 (d, J = 9.00 Hz, 1 H), 4.19 (s, 1 H), 2.30–2.15 (m, 2 H), 1.75–1.45 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5 (s), 132.1 (d), 128.1 (d), 124.2 (s), 120.3 (s), 115.6 (d), 111.8 (s), 53.4 (s), 35.9 (t, 2C), 24.6 (t), 21.8 (t, 2C).

MS (EI, 70 eV): m/z = 285 (M^+ – HCN, 56), 287 (71), 244 (100), 242 (78), 191 (16), 189 (12).

2-[(2-Bromophenyl)amino]butanenitrile (5):
Propionaldehyde (0.36 mL, 5 mmol) was added dropwise to 2-bromoaniline (0.86 g, 5 mmol) and the mixture was stirred for 24 h. EtOH (10 mL) was added to the crude aldimine and the solution was treated with trimethylsilyl cyanide (1.3 mL, 10 mmol). After 48 h reflux, the solution was cooled, concentrated, and the crude reaction mixture which was purified by flash chromatography; yield: 0.48 g (40%); R_f 0.55 (EtOAc/cyclohexane, 10:90).

IR (film): ν = 3460, 2240 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (dd, J = 7.72, 1.47 Hz, 1 H), 7.29 (td, J = 7.72, 1.47 Hz, 1 H), 6.86–6.72 (m, 2 H), 4.54 (d, J = 8.00 Hz, 1 H), 4.16 (td, J = 8.00, 7.35 Hz, 1 H), 1.98 (quint, J = 7.35 Hz, 2 H), 1.19 (t, J = 7.35 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1 (s), 132.4 (d), 128.4 (d), 119.2 (d), 119.1 (s), 115.8 (d), 110.6 (s), 46.8 (d), 26.5 (t), 10.1 (q).

MS (EI; 70 eV): m/z = 238 (M^+, 26), 240 (26), 211 (100), 209 (92).

(2-Alkylamino)benzonitriles 6–10; General Procedure:

AIBN (0.1 equiv) and Bu_3SnH (2 equiv) were added to a stirred solution of the appropriate α-aminonitrile **1–5** (0.03 equiv) in toluene. The reaction was monitored by TLC. After 1 h reflux (except for **1**, 20 h), the toluene was evaporated in vacuo and the residue was purified by flash chromatography.

2-[(1-Ethylpropyl)amino]benzonitrile **(6)**; oil; yield: 58%; R_f 0.55 (EtOAc/cyclohexane; 10:90).

IR (film): ν = 3400, 2210 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 6.56 (d, J = 9.19 Hz, 1 H), 6.54 (dd, J = 9.80, 2.50 Hz, 1 H), 4.25 (d, J = 8.00 Hz, 1 H), 3.16 (quint d, J = 8.00, 6.80 Hz, 1 H), 1.65–1.35 (m, 4 H), 0.88 (t, J = 7.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4 (s), 134.0 (d), 132.7 (d), 117.9 (s), 115.6 (d), 110.8 (d), 95.2 (s), 55.3 (d), 26.7 (t, 2C), 9.9 (q, 2C).

MS (EI; 70 eV): m/z = 188 (M^+, 13), 160 (11), 159 (100), 132 (13).

2-(Cyclopentylamino)benzonitrile **(7)**; oil; yield: 65%; R_f 0.57 (EtOAc/cyclohexane, 20:80).

IR (film): ν = 3400, 2210 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 2 H), 6.63 (d, J = 8.50 Hz, 1 H), 6.60 (dd, J = 8.50, 1.07 Hz, 1 H), 4.40 (br s, 1 H), 3.85–3.70 (m, 1 H), 2.05–1.90 (m, 2 H), 1.75–1.20 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8 (s), 133.9 (d), 132.5 (d), 117.8 (s), 115.9 (d), 111.2 (d), 95.4 (s), 54.1 (d), 33.2 (t), 26.6 (t), 23.8 (t), 17.2 (t).

MS (EI, 70 eV): m/z = 186 (M^+, 32), 157 (100), 144 (22), 118 (30).

2-(Cyclohexylamino)benzonitrile **(8)**; solid, mp 69–70°C; yield: 60%; R_f 0.58 (EtOAc/cyclohexane, 15:85).

IR (film): ν = 3400, 2210 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 2 H), 6.67 (d, J = 8.25 Hz, 1 H), 6.62 (td, J = 8.25, 1.10 Hz, 1 H), 4.47 (br s, 1 H), 3.43–3.29 (m, 1 H), 2.10–1.99 (m, 2 H), 1.87–1.73 (m, 2 H), 1.71–1.59 (m, 2 H), 1.57–1.29 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.3 (s), 133.9 (d), 132.7 (d), 117.9 (s), 115.7 (d), 110.8 (d), 95.3 (s), 51.2 (d), 32.8 (t, 2C), 25.6 (t), 24.6 (t, 2C).

MS (EI, 70 eV): m/z = 200 (M^+, 24), 157 (100), 144 (12), 118 (25).

5-Chloro-2-(cyclohexylamino)benzonitrile **(9)**; oil; yield: 45%; R_f 0.58 (EtOAc/cyclohexane, 15:85).

IR (film): ν = 3400, 2210 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (dd, J = 2.58, 0.74 Hz, 1 H), 7.26 (dd, J = 9.01, 2.58 Hz, 1 H), 6.60 (d, J = 9.01 Hz, 1 H), 4.58 (s, 1 H), 3.34–3.22 (m, 1 H), 2.05–1.95 (m, 2 H), 1.83–1.71 (m, 2 H), 1.69–1.58 (m, 2 H), 1.45–1.16 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9 (s), 134.1 (d), 131.6 (d), 120.0 (s), 116.7 (s), 112.2 (d), 96.2 (s), 51.4 (d), 32.6 (t, 2C), 25.4 (t), 24.6 (t, 2C).

MS (EI; 70 eV): m/z = 234 (M^+, 35), 236 (12), 193 (32), 191 (100), 152 (47).

2-(Propylamino)benzonitrile **(10)**;[8] oil; yield: 45%; R_f 0.58 (EtOAc/cyclohexane ; 10:90),

IR (film): ν = 3380, 2210 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 6.65 (d, J = 8.45 Hz, 1 H), 6.63 (td, J = 6.80, 1.10 Hz, 1 H), 4.53 (br s, 1 H), 3.15 (t, J = 7.35 Hz, 2 H), 1.67 (sext, J = 7.35 Hz, 2 H), 1.00 (t, J = 7.35 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4 (s), 134.2 (d), 132.7 (d), 117.9 (s), 116.9 (d), 110.5 (d), 95.3 (s), 45.0 (t), 22.3 (t), 11.4 (q).

MS (EI; 70 eV): m/z = 160 (M^+, 23), 131 (100), 104 (10).

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(1) Kalvoda, J. *Helv. Chim. Acta* **1968**, *51*, 267.
Kalvoda, J. *J. Chem. Soc., Chem. Commun.* **1970**, 1002.
Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.
Kalvoda, J.; Botta, L. *Helv. Chim. Acta* **1972**, *55*, 356.
Watt, D.S. *J. Am. Chem. Soc.* **1976**, *98*, 271.
Freerksen, R.W.; Pabst, W.E.; Raggio, M.L.; Sherman, S.A.; Wroble, R.R.; Watt, D.S. *J. Am. Chem. Soc.* **1977**, *99*, 1536.
Barone, A.D.; Watt, D.S. *Tetrahedron Lett.* **1978**, 3673.
Wolff, S.; Agosta, W.C. *J. Org. Chem.* **1978**, *43*, 3627.
Burry, A.; Bougeard, P.; Corker, S.J.; Johnson, M.D.; Perlmann, M. *J. Chem. Soc., Perkin Trans 2* **1982**, 1367.

(2) Clive, D.L.J.; Beaulieu, P.L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313.

(3) Ogibin, Y.N.; Troyanskii, E.I.; Nikishin, G.I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 1461; *Chem. Abstr.* **1975**, *83*, 96475.
Ogibin, Y.N. Troyanskii, E.I.; Nikishin, G.I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 843; *Chem. Abstr.* **1977**, *87*, 52835.
Griller, D.; Schmid, P.; Ingold, K.U. *Can. J. Chem.* **1979**, *57*, 831.
Roberts, B.P.; Winter, N.J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1353.
Corey, E.J.; Pine, S.G. *Tetrahedron Lett.* **1983**, *24*, 2821.

(4) Hawthorne, D.G.; Johns, S.R.; Solomon, D.H.; Willing, R.I. *J. Chem. Soc., Chem. Commun.* **1975**, 982.
Hawthorne, D.G.; Johns, S.R.; Willing, R.I. *Aust. J. Chem.* **1976**, *29*, 315.

(5) Chenera, B.; Chuang, C.P.; Hart, D.J.; Hsu, L.Y. *J. Org. Chem.* **1985**, *50*, 5409.

(6) Beckwith, A.L.J.; O'Shea, D.M.; Gerba, S.; Westwood, S.W. *J. Chem. Soc., Chem. Commun.* **1987**, 666.
Beckwith, A.L.J.; O'Shea, D.M.; Westwood, S.W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.
Curran, D.P.; Seong, C.M. *J. Am. Chem. Soc.* **1990**, *112*, 9401.
Callier, A.C.; Quielet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* **1994**, *35*, 6109.

(7) The alkylation of α-aminobenzonitrile with secondary alkyl bromides or non-activated primary alkyl bromides gave a poor yield of 2-(alkylamino)benzonitriles.

(8) Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Heterocycl. Chem.* **1980**, *17*, 155.

(9) Tiollais, R. *Bull. Soc. Chim. Fr.* **1947**, 708.
Feldman, P.L.; Backeen, M.F. *J. Org. Chem.* **1990**, *55*, 4207.

(10) Davis, F.A.; Venkat Reddy, G.; Bental, M.; Deutsch, C.J. *Synthesis* **1994**, 701.

(11) Bruson, H.A.; Plant, H.L. *J. Org. Chem.* **1967**, *32*, 3356.

(12) Egger, K.W.; Cocks, A.T. *Helv. Chim. Acta* **1973**, *56*, 1516.
O'Neal, H.E.; Benson, S.W. *Free Radical*; Kochi, J.K. Ed.; Wiley: New York, 1973.
Mc Millen, D.F.; Golden, D.M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493.

(13) Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(14) Substituted 2-bromoanilines and ketones were refluxed in benzene with azeotropic removal of water.