Nucleophilic Aromatic Substitution Reactions of Chloroanilines and Chloroanilides with Potassium Phenyl Thiolate

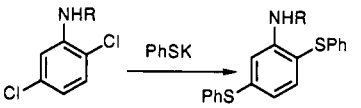
Andrew J. Caruso,* Alice M. Colley, and Gary L. Bryant

GE Corporate Research and Development Center, Schenectady, New York 12301

Received June 21, 1990

Alkyl and aryl thiolates are known to effect halogen displacement in reactions with unactivated or slightly activated mono- and polyhalogenobenzenes under several sets of conditions. Copper(I) thiolates,[1] thiolate salts of lead, zinc, and mercury,[2] alkali metal thiolates under photostimulation[3] or in the presence of nickel(II),[4] palladium(0),[5] or phase-transfer[6] catalysts all react with unactivated aryl halides to afford alkyl aryl sulfides and diaryl sulfides. In many instances, simply heating an aryl halide with the sodium or potassium salt of an alkyl or aryl thiol in a polar, aprotic solvent is sufficient to effect this substitution reaction.[7] In connection with another study, we were intrigued by the possibility of using simple chloroanilines as the electrophile in aromatic substitution reactions of this type, a prospect clouded initially by the deactivating character of the amino group under such circumstances.[8] Cuprous phenyl thiolate[1b] and cuprous ethyl thiolate[1c] have been shown to effect halogen displacement with 4-chloro- and 4-bromoaniline, respectively, and several examples of copper-mediated substitution reactions of simple haloanilides are known.[1a-c] Moreover, 4-bromoaniline has been reported to afford 4-(phenylthio)aniline upon exposure at high temperature to sodium phenylthiolate in the presence of *o*-phenylenebis[diphenylphosphine]nickel(II).[4] The corresponding uncatalyzed reactions of simple alkyl or aryl alkali metal thiolates with chloroanilines or chloroanilides lacking other activating functional groups appear to be unknown. We now report that a variety of chloroanilines, as well as their *N*-acetyl and *N*-pivaloyl derivatives, react smoothly with potassium phenyl thiolate in 1-methyl-2-pyrrolidinone (NMP) at temperatures ranging from 140 to 190 °C to afford a number of hitherto unrecorded (phenylthio)anilines or the corresponding anilides. This observation has allowed the preparation of (phenylthio)anilines not accessible by the classical stratagem of nitro group activation of suitable ortho and/or para leaving groups, displacement, and reduction[9] and avoids the necessity of using copper or nickel reagents in the more direct displacement route. A marked activating effect of an *N*-acyl moiety may be used to advantage in instances of recalcitrant chloroanilines and allows selective monosubstitution in the case of *N*-acyl-2,4-dichloroanilines.

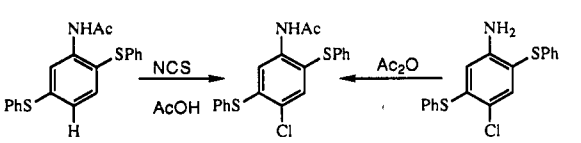
Initially we examined the reactivity of 2,5-dichloroaniline (1) with potassium phenyl thiolate. While 1 failed to react upon exposure to excess thiophenol and potassium carbonate at 140 °C in NMP, higher reaction temperature (190 °C) and a somewhat longer reaction time (26 h) afforded 2,5-bis(phenylthio)aniline (2) in excellent (90%) yield. The use of *N*,*N*-dimethylacetamide as the solvent for this reaction at 140 °C after 24 h gave anilide 4 in



1 R=H 2 R=H
3 R=Ac 4 R=Ac

modest (20%) yield via a transformation thought to involve acylation of the starting aniline by the solvent followed by substitution of chlorine by phenyl thiolate.[10] Not surprisingly, dichloroanilide 3 underwent smooth reaction with potassium phenyl thiolate at 140 °C to give bis(phenylthio)anilide 4 in 90% yield after 18 h. Having demonstrated that nucleophilic aromatic substitution of chlorine in chloroanilines such as 1 by phenyl thiolate is possible and taking note of the enhanced reactivity of the anilides, we set out to explore the scope of this displacement chemistry. Data gathered from reaction between potassium phenyl thiolate and a series of mono-, di-, and trichloroanilines and anilides are given in Table I. Yields refer to isolated, crystalline materials and have not been optimized. Yields given in parentheses refer to contained yield.

Among the chloroanilines investigated the most favorable combination of substrate reactivity and ease of product isolation was observed for 2,5- and 2,3-dichloroaniline and 3,4,5-trichloroaniline (compounds 1, 5, and 21, respectively). In general, however, crude products were obtained as mixtures and required separation via reversed-phase medium-pressure chromatography and/or fractional crystallization. Under the reaction conditions employed trichloroanilines 15 and 18 afforded 1:1 mixtures of the bis- and tris(phenylthio)anilines shown. While the ^1H and ^{13}C NMR spectra of 4-chloro-2,6-bis(phenylthio)aniline (19) are unambiguous, the assignment of regiochemistry in the case of compound 16 is based on its correlation (^1H NMR) with the ring chlorination product (*N*-chlorosuccinimide, AcOH, reflux) of bis(phenylthio)anilide 4.



4 25 16

(1) (a) Tarbell, D. S.; Todd, C. W.; Paulson, M. C.; Lindstrom, E. G.; Wystrach, V. P. *J. Am. Chem. Soc.* **1948**, *70*, 1381. (b) Adams, R.; Reifschneider, W.; Nair, M. D. *Croatica Chem. Acta* **1957**, *29*, 277. (c) Adams, R.; Ferretti, A. *J. Am. Chem. Soc.* **1959**, *81*, 4927. (d) Campbell, J. R. *J. Org. Chem.* **1962**, *27*, 2207. (e) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1108. (f) Fujihara, H.; Chiu, J.; Furukawa, N. *J. Am. Chem. Soc.* **1988**, *110*, 1280.

(2) For examples and references, see: Schöberl, A.; Wagner, A. *Houben-Weyl, Methoden der Organischen Chemie*, Georg Thieme Verlag: Stuttgart, 1955; Vol. IX, p 97.

(3) (a) Bunnett, J. F.; Creary, X. *J. Org. Chem.* **1974**, *39*, 3173. (b) *Ibid.* **1974**, *39*, 3611.

(4) Cristau, H. J.; Chabaud, B.; Chêne, A.; Christol, H. *Synthesis* **1981**, 892.

(5) Migita, T.; Shimzu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.

(6) (a) Landini, D.; Montanari, F.; Rolla, F. *J. Org. Chem.* **1983**, *48*, 604. (b) Brunelle, D. J. *Ibid.* **1984**, *49*, 1309.

(7) (a) Campbell, J. R.; Hatton, R. E. *J. Org. Chem.* **1961**, *26*, 2480. (b) Uhlenbroek, J. H. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1057. (c) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830. (d) Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *Ibid* **1979**, *44*, 2642. (e) Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* **1980**, *21*, 3099. (f) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751. (g) West, A. P., Jr.; Van Engen, D.; Pascal, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 6846.

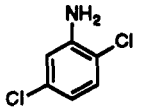
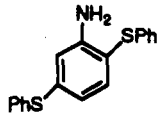
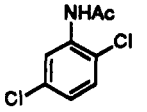
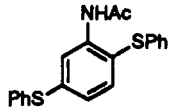
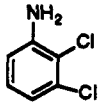
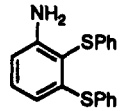
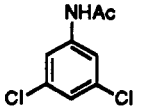
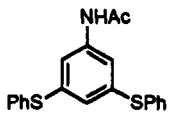
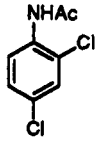
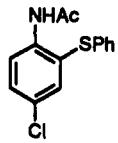
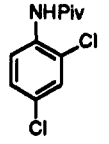
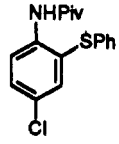
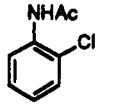
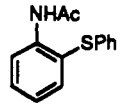
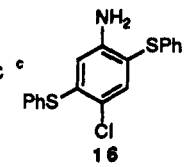
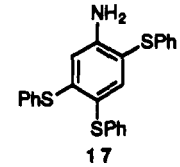
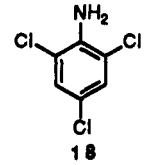
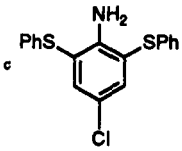
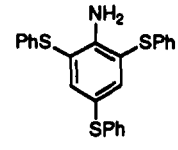
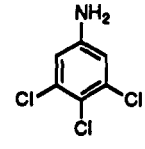
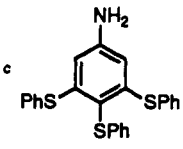
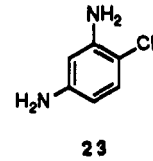
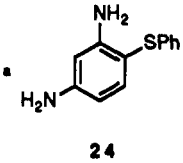
(8) (a) Berliner, E.; Monack, L. C. *J. Am. Chem. Soc.* **1952**, *74*, 1574. (b) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968; p 88.

(9) (a) Bourgeois, E.; Huber, P. *Recl. Trav. Chim. Pays-Bas* **1912**, *31*, 30. (b) Miller, R. F.; Turley, J. C.; Martin, G. E.; Williams, L.; Hudson, J. E. *Synth. Commun.* **1978**, *8*, 371.

(10) It is tempting to invoke a similar but catalytic role for NMP at higher temperature for the transformation of chloroanilines to the corresponding (phenylthio)anilines.

0022-3263/91/1956-0862$02.50/0

Table I. Substrates, Products, Reaction Conditions, and Yields

chloroaniline or chloroanilide	reaction time/ temp	product(s)	isolated yield
 1	26 h / 190° C [a]	 2	90%
 3	18 h / 140°C [a]	 4	90%
 5	48 h / 140°C [a]	 6	57%
 7	92 h / 140°C [a]	 8	37%
 9	3 h / 165°C [b]	 10	60%
 11	2 h / 170°C [b]	 12	89%
 13	48 h / 180°C [b]	 14	40%
 15	96 h / 160°C [c]	 16	8%
		 17	8%
 18	28 h / 170°C [c]	 19	(48%)
		 20	(39%)
 21	48 h /190°C [c]	 22	26%
 23	24 h / 190°C [a]	 24	24%

[a] 2.53 equiv of PhSH, 4.0 equiv of K_2CO_3. [b] 1.05 equiv of PhSH, 2.0 equiv of K_2CO_3. [c] 3.78 equiv of PhSH, 6.0 equiv of K_2CO_3. [d] Parentheses indicate contained yield.

That 4-chloro-1,3-phenylenediamine (**23**) undergoes reaction with potassium phenyl thiolate is of interest in that this should be a particularly disfavored substrate for nucleophilic aromatic substitution. A number of other aniline substrates (4-chloroaniline and 2,4-, 3,4-, and 3,5-dichloroaniline) afforded mixtures upon prolonged exposure to potassium phenyl thiolate from which we were unable to obtain product (phenylthio)anilines in rigorously pure form. Monochloroanilines were generally found to be poor substrates for this reaction, although 2-chloroaniline appeared to be somewhat more reactive than the 3- or 4-chloro derivatives.

As noted earlier we had observed an enhancement in the reactivity of 2,5-dichloroacetanilide (**3**) with potassium phenyl thiolate relative to the corresponding free aniline. We sought to use this observation to prepare phenylthio derivatives from less reactive substrates such as monochloroanilines and 2,4-, 3,4-, and 3,5-dichloroaniline. Moreover, we wished to learn more about the sequence of chloride displacement in reactions of multiply substituted chloroanilines and its implications for selectivity in this series. Among the monochloroanilides only 2-chloroacetanilide reacted at a synthetically useful rate under the conditions employed. In contrast to 3,5-dichloroaniline, 3,5-dichloroacetanilide (**7**) underwent smooth reaction with potassium phenyl thiolate and gave the bis(phenylthio)-anilide **8** in pure form after a single crystallization. In reactions of 2,4-dichloroacetanilide (**9**) or the corresponding

N-pivaloyl derivative **11** with a slight excess (1.05 equiv) of phenyl thiolate with noted (HPLC) rapid formation of a single monosubstituted product containing a few percent of the corresponding disubstituted product and starting material. In each case we obtained the 4-chloro-2-(phenylthio)anilide **10** or **12** in good yield following recrystallization. Single-crystal X-ray analysis provided an unambiguous assignment of regiochemistry in the case of product **12**.

The regioselectivity displayed in displacement reactions of anilides **9** and **11** is of interest in that it is significantly greater than that observed for the corresponding reaction of potassium phenyl thiolate with 2,4-dichloronitrobenzene.[11,12] Anilides **9** and **11** were considerably more reactive than 2-chloroacetanilide (**13**) which in a control experiment afforded a 1:1 mixture of the substitution product **14** and starting material after 10 h at 165 °C. In preparative experiments (Table I) a longer reaction time (48 h) and higher temperature (180 °C) were used.

This study demonstrates that chloroanilines, and to a greater degree chloroanilides, arylate potassium phenyl thiolate in NMP at temperatures ranging from 140 to 190 °C, affording a variety of (phenylthio)anilines and anilides not readily accessible by other means. Catalysis by copper or nickel is not required. Monochloroanilines are poor substrates for this reaction, but a number of di- and trichloroanilines react smoothly to give bis- and tris(phenylthio)anilines. Under the conditions examined in this study chloroanilides were generally more reactive than their aniline counterparts. This activation by an *N*-acyl moiety represent a new and synthetically useful tool for the preparation of amine-substituted aryl sulfides.

Experimental Section

General Procedures. Melting points are uncorrected. Infrared spectra were recorded as KBr pellets. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on a GE-QE 300 instrument. Reversed-phase MPLC refers to chromatography done at 10–50 psi through EM Lobar columns packed with Baker Octadecyl (C18) 40-μm bulk packing for flash chromatography and monitored by ultraviolet detection at 254 nm. Reaction progress was followed by HPLC and/or reversed-phase thin-layer chromatography.

(Phenylthio)anilines and Anilides. General Method. To a two-neck, 100-mL round-bottomed flask equipped with a condenser and nitrogen inlet was added the chloroaniline or chloroanilide derivative (19.23 mmol), dry NMP (50 mL), and freshly distilled thiophenol (1.05–3.78 equiv, see Table I). The apparatus was then purged thoroughly with N_2, and solid K_2CO_3 (2.5–6.0 equiv, see Table I) was added rapidly under N_2. The flask was then heated in an oil bath at 140–190 °C for a period of 2–96 h while the contents of the flask were stirred magnetically. Specific reaction times and temperatures are given in Table I. After cooling to ambient temperature the reaction mixture was diluted with ethyl ether (200 mL) and water (200 mL) and the organic phase was washed with 5% NaOH (3 × 100 mL), water (1×), and brine (1×), dried ($MgSO_4$), and concentrated under reduced pressure. Crude products were purified by reverse-phase MPLC and/or recrystallization.

2,5-Bis(phenylthio)aniline (2). Workup afforded crude (**2**) (5.360 g, 17.32 mmol, 90%) as a dark, viscous oil which crystallized on standing. Recrystallization (MeOH) afforded an analytical sample (tan solid): mp 60–61 °C; ^1H NMR δ 7.51–7.43 (m, 2), 7.39–7.26 (m, 4), 7.25–7.16 (m, 2), 7.15–7.02 (m, 3), 6.61 (br d, 1, J = 2), 6.60 (dd, 1, J = 2, 8.5), 4.23 (br s, 2); IR 3465, 3370, 1600, 1582, 1478, 1470, 1405, 1075, 1025, 740, 690 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NS_2$: C, 69.86; H, 4.89; N, 4.53. Found: C, 69.90; H, 4.89; N, 4.54.

2,5-Bis(phenylthio)acetanilide (4). Compound **4** was obtained (6.112 g, 17.39 mmol, 90%) as a light brown oil which crystallized on standing. Recrystallization (hexane–EtOAc) afforded an analytical sample: mp 65–67 °C; ^1H NMR δ 8.37 (br s, 1), 8.14 (br s, 1), 7.53–7.05 (m, 11), 6.88 (dd, 1, J = 2, 8), 2.00 (s, 3); IR 3200, 3050, 1655, 1575, 790, 745, 735 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NOS_2$: C, 68.34; H, 4.88; N, 3.99. Found: C, 68.24; H, 4.96; N, 4.07.

2,3-Bis(phenylthio)aniline (6). The crude product was recrystallized (MeOH) to afford analytically pure material (3.383 g, 10.93 mmol, 57%): mp 96–98.5 °C; ^1H NMR δ 7.48 (m, 2), 7.36 (m, 3), 7.25 (m, 2), 7.14 (m, 3), 7.01 (t, 1, J = 8), 6.55 (dd, 1, J = 1, 8), 6.20 (dd, 1, J = 1, 8 Hz), 4.42 (br s, 2); IR 3465, 3370, 3355, 3050, 1600, 1475, 1455, 1280, 1025, 770, 755, 740, 720, 690 cm^{-1}. Anal. Calcd for $C_{18}H_{15}HNS_2$: C, 69.86; H, 4.89; N, 4.53. Found: C, 69.70; H, 4.80; N, 4.46.

3,5-Bis(phenylthio)acetanilide (8). Recrystallization (MeOH) afforded pure **8** (2.49 g, 7.08 mmol, 37%) mp 99–99.5 °C; ^1H NMR δ 7.72 (br s, 1), 7.38–7.18 (m, 12), 6.86 (t, 1, J = 1.5), 2.05 (s, 3); IR 3290, 3250, 1660, 1595, 1575, 1535, 1400, 1280, 890, 845, 790, 740 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NOS_2$: C, 68.34; H, 4.88; N, 3.99. Found: C, 68.11; H, 4.76; N, 3.92.

4-Chloro-2-(phenylthio)acetanilide (10). Scale was 1.8-fold greater than that described in the general procedure. Recrystallization (MeOH) afforded **10** (5.69 g, 20.49 mmol, 60%) as a white crystalline solid: mp 120–122 °C; ^1H NMR δ 8.38 (d, 1, J = 9), 8.07 (br s, 1), 7.53 (d, 1, J = 2), 7.38 (dd, 1, J = 2, 9), 7.33–7.18 (m, 3), 7.12 (br d, 2, J = 8), 2.05 (s, 3); IR 3280, 1665, 1575, 1510, 1380, 1295, 1100, 885, 830, 750, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{12}ClNOS$: C, 60.53; H, 4.36; N, 5.04. Found: C, 60.21; H, 4.27; N, 4.82.

***N*-Pivaloyl-4-chloro-2-(phenylthio)aniline (12).** Workup afforded **12** (5.47 g, 17.10 mmol, 89%) as an off-white crystalline solid. Recrystallization (MeOH) gave an analytical sample: mp 81–82 °C (crystals suitable for X-ray analysis); ^1H NMR δ 8.48 (d, 1, J = 9), 8.47 (br s, 1), 7.59 (d, 1, J = 2.5), 7.41 (dd, 1, J = 2.5, 9), 7.29–7.23 (m, 2), 7.21–7.15 (m, 1), 7.08–7.04 (m, 2), 1.10 (s, 9); IR 3255, 2970, 1645, 1515, 1465, 1095, 1060, 865, 820, 800, 750, 690 cm^{-1}. Anal. Calcd for $C_{17}H_{18}ClNOS$: C, 63.84; H, 5.67; N, 4.38. Found: C, 63.90; H, 5.68; N, 4.28.

2-(Phenylthio)acetanilide (14). The scale was 2.5-fold greater than that described in the general procedure. Workup gave initially a yellow solid (9.76 g). Recrystallization (MeOH) afforded **14** (4.67 g, 19.19 mmol, 40%) as a white crystalline solid: mp 92–94 °C (lit.[13] mp 96.5–97 °C); ^1H NMR δ 8.43 (br d, 1, J = 8), 8.18 (br s, 1), 7.57 (dd, 1, J = 1.5, 8), 7.47 (br ddd, 1, J = 2, 8, 8), 7.30–7.05 (m, 6), 2.04 (s, 3); IR 3320, 1680, 1575, 1510, 1440, 1295, 1240, 750, 690, 670, 600 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.10; H, 5.38; N, 5.76. Found: C, 68.89; H, 5.35; N, 5.74.

4-Chloro-2,5-bis(phenylthio)aniline (16) and 2,4,5-Tris(phenylthio)aniline (17). Workup afforded a 1:1 mixture (^1H NMR) of **16** and **17** (7.02 g), as a dark oil which solidified on standing. Trituration of the solid with hot methanol gave a sample (760 mg) of the bis(phenylthio) derivative **16** containing about 5% of trisphenylthio derivative **17**. Recrystallization (hexane–EtOAc) furnished analytically pure **16** (550 mg, 1.60 mmol, 8%): mp 106–108 °C; ^1H NMR δ 7.52 (m, 2), 7.44 (s, 1), 7.42 (m, 3), 7.23 (br t, 2, J = 8), 7.13 (br t, 1, J = 8), 7.08 (br d, 2, J = 8), 6.18 (s, 1), 4.13 (br s, 2); IR 3460, 3450, 3370, 3360, 1605, 1580, 1480, 1455, 1440, 1380, 1250, 1020, 930, 755, 745, 690 cm^{-1}. Anal. Calcd for $C_{18}H_{14}ClNS_2$: C, 62.87; H, 4.10; N, 4.07. Found: C, 62.82; H, 4.11; N, 4.04. Recombination and concentration of the filtrates generated above afforded a dark solid which when triturated with hot methanol gave trisulfide **17** (680 mg, 1.63 mmol, 8%) as a tan powder. Recrystallization (EtOAc–hexane) afforded an analytical sample: mp 140–142 °C; ^1H NMR δ 7.66 (s, 1), 7.52 (m, 2), 7.40 (m, 3), 7.30–7.05 (m, 10), 6.15 (s, 1), 4.30 (br s, 2); IR 3470, 3370, 1600, 1580, 1475, 1450, 1440, 1380, 1025, 750, 735, 690 cm^{-1}. Anal. Calcd for $C_{24}H_{19}NS_3$: C, 69.03; H, 4.59; N, 3.35. Found: C, 68.83; H, 4.59; N, 3.34.

(11) (a) Bunnett, J. F.; Morath, R. J. *J. Am. Chem. Soc.* **1955**, *77*, 5051. (b) Leandri, G.; Tundo, A. *Ann. Chim.* **1954**, *44*, 271.

(12) In our hands reaction of 2,4-dichloronitrobenzene with 1 equiv of potassium phenyl thiolate in dimethylacetamide at ambient temperature afforded both possible monosubstituted products, 2,4-bis(phenylthio)-nitrobenzene and starting dichloronitrobenzene as a 2.9 (2-PhS-):1.4 (4-PhS-):1.0 (2,4-$(PhS)_2$):1.3 (2,4-$(Cl)_2$) mixture.

(13) Jilek, J. O.; Pelz, K.; Pavlickova, D.; Protiva, M. *Collect. Czech. Chem. Commun.* **1965**, 430, 1676.

4-Chloro-2,6-bis(phenylthio)aniline (19) and 2,4,6-Tris(phenylthio)aniline (20). Workup afforded a 1:1 mixture (^{1}H NMR) of **19** and **20** (6.96 g) as a dark oil. A portion (398 mg) of this material was subjected to reverse-phase MPLC (3:1 acetonitrile–water) to give first 2,6-bis(phenylthio)-4-chloroaniline (**19**) (183 mg, 0.53 mmol) as a burgundy solid followed by 2,4,6-tris(phenylthio)aniline (**20**) (179 mg, 0.43 mmol) as an off-white solid. Recrystallization (EtOAc–hexane) afforded analytical samples of each. **19**: mp 106–110 °C; ^{1}H NMR δ 7.51 (s, 2), 7.30–7.03 (m, 10), 4.95 (br s, 2); ^{13}C NMR 148.96, 137.59, 134.90, 129.22, 127.20, 126.25, 121.51, 116.71; IR 3455, 3350, 3250, 1590, 1580, 1475, 1435, 730, 720, 688 cm^{-1}. Anal. Calcd for $C_{18}H_{14}ClNS_2$: C, 62.87; H, 4.10; N, 4.07. Found: C, 62.49; H, 4.02; N, 4.03. **20**: mp 84–87 °C; ^{1}H NMR δ 7.71 (s, 2), 7.30–7.00 (m, 15), 5.07 (br s, 2); IR 3485, 3380, 3250, 1582, 1478, 1440, 735, 688 cm^{-1}. Anal. Calcd for $C_{24}H_{19}NS_3$: C, 69.03; H, 4.59; N, 3.35. Found: C, 69.00; H, 4.57; N, 3.35.

3,4,5-Tris(phenylthio)aniline (22). The scale was 0.5-fold less than that described in the general procedure. Workup gave a partially crystalline mass (2.96 g) which was triturated with hot MeOH (250 mL), giving **22** (1.04 g, 2.48 mmol, 26%) as an off-white solid. Recrystallization (EtOAc–cyclohexane) provided an analytical sample: mp 158–160 °C; ^{1}H NMR δ 7.50 (m, 4), 7.39 (m, 6), 7.31–7.24 (m, 2), 7.22–7.10 (m, 3), 5.84 (s, 2), 3.53 (br s, 2); IR 3475, 3380, 3060, 1618, 1570, 1535, 1480, 1440, 1415, 1290, 1025, 830, 795, 758, 750, 738, 705, 690 cm^{-1}. Anal. Calcd for $C_{24}H_{19}NS_3$: C, 69.03; H, 4.59; N, 3.35. Found: C, 69.17; H, 4.61; N, 3.40.

4-(Phenylthio)-1,3-phenylenediamine (24). The reaction was carried out on the hemisulfate of 4-chloro-1,3-phenylenediamine (**23**). Workup afforded crude **24** as a brown solid (1.97 g). Recrystallization (MeOH) afforded analytically pure material (997 mg, 4.61 mmol, 24%): mp 103–104.5 °C; ^{1}H NMR δ 7.24–7.15 (m, 2), 7.23 (d, 1, J = 8.1), 7.09–7.02 (m, 3), 6.10 (dd, 1, J = 2.3, 8.1), 6.07 (d, 1, J = 2.3), 4.20 (br s, 2), 3.72 (br s, 2); IR 3430, 3380, 1610, 1490, 1475, 1440, 1325, 1260, 855, 735 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.62; H, 5.59; N, 12.95.

Supplementary Material Available: Structure, crystal data, atomic cooridnates, bond lengths and angles, anisotropic displacement coefficients, and H atom coordinates for **12** (11 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole: A Novel Reissert Compound from Benzimidazole[1]

Yajnanarayana H. R. Jois and Harry W. Gibson*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

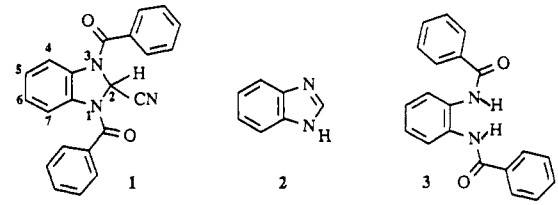
Received June 15, 1990

Introduction

Since their discovery by Arnold Reissert,[2a] Reissert compounds, α-acylaminonitriles, have proven useful as intermediates in the synthesis of various heterocyclic compounds, such as derivatives of isoquinoline, quinoline, quinazoline, etc., including alkaloids and other biologically active compounds.[2] During the course of synthetic studies for the preparation of specialty heterocyclic polymers,[3] we had the occasion to investigate methods of incorporating heterocycles via Reissert chemistry.

One of the requirements for polymer synthesis is the presence of difunctionality in the starting materials. Benzimidazoles are difunctional in the sense that via Reissert compound formation two amide linkages can be formed, e.g., as in **1**. Further, benzimidazoles are inexpensive, commercially available materials. This potential has led us to investigate the scope and limitations of the Reissert reaction of benzimidazoles with the expectation that this process could serve as a simple and expedient method for the synthesis of polybenzimidazoles.

However, little is known about benzimidazole Reissert compounds, although a carbamate analog was reported by Uff et al.[4] In the two phase (dichloromethane–water) system, the Reissert reaction of benzoyl chloride and KCN with benzimidazole (**2**), with or without phase-transfer catalyst, is reported to yield *o*-phenylenedibenzamide[5] (**3**). In a very recent publication, Uff et al.[6] claim the synthesis of **1**. However, we have obtained totally different results in our laboratory and report them here.



Results and Discussion

A. Direct Reaction of Benzimidazole. Our first approach to the synthesis of 2-cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole (**1**) (Scheme I) was the direct Reissert reaction of benzimidazole (**2**) in a range of anhydrous solvents (dichloromethane, dioxane, *N*-methylpyrrolidinone, tetrahydrofuran) with 2 equiv of benzoyl chloride in presence of trimethylsilyl cyanide (TMSCN) and a suitable base like triethylamine or pyridine. This led mainly to 1-benzoylbenzimidazole (**4**) along with the desired product **1** in trace amounts, probably because of the similar basicities of the second nitrogen in benzimidazole and the acid acceptors used.

B. Reactions of 1-Benzoylbenzimidazole. To obtain a better yield of the desired product **1**, we approached the synthesis by a two-step process. In the first step, we prepared 1-benzoylbenzimidazole (**4**) from benzimidazole by reaction with benzoyl chloride in the presence of triethylamine in *N*,*N*-dimethylformamide (DMF) (80% yield).

a. Use of Dichloromethane–Water Method. 1-Benzoylbenzimidazole (**4**) with benzoyl chloride and KCN in dichloromethane–water yielded a new product in excellent yield. The melting point of this product (**5**) (159–60 °C) was much lower than that of *o*-phenylenedibenzamide (**3**) (lit.[7] mp 301–4 °C). The infrared spectrum of **5** showed NH as well as three carbonyl absorptions. ^{1}H and ^{13}C NMR showed one of the carbonyl groups to be a formyl function. Additional information obtained from ^{1}H NMR, MS, and CHN analysis of the product conclusively proved

(1) This work was presented orally in the Organic Division, 199th ACS National meeting, April 22–27, 1990, paper no. 441.

(2) (a) Reissert, A. *Chem. Ber.* **1905**, *38*, 1603. (b) Popp, F. D. *Heterocycles* **1973**, *1*, 165. (c) Popp, F. D. *Adv. Heterocycl. Chem.* **1979**, *24*, 187. (d) Cooney, J. V. *J. Heterocycl. Chem.* **1983**, *20*, 823. (e) Vorbruggen, H.; Maas, M. *Heterocycles* **1988**, *27*, 2659. (f) Knabe, J. *Adv. Heterocyl. Chem.* **1986**, *40*, 105.

(3) (a) Jois, Y. H. R.; Gibson, H. W. *Am. Chem. Soc. Polymer Preprints* **1990**, *31*(1), 474. (b) Gibson, H. W.; Guilani, B. *Macromolecules* **1990**, *23*, 4339. (c) Gibson, H. W.; Pandya, A.; Guilani, B.; Rasco, M. L.; Jois, Y. H. R. *Polymer Commun.*, in press.

(4) Uff, B. C.; Ho, Y. P.; Burford, D. L. W.; Popp, F. D. *J. Heterocycl. Chem.* **1987**, *24*, 1349.

(5) Battacharjee, D.; Popp, F. D. *J. Heterocycl. Chem.* **1980**, *17*, 1211.

(6) Uff, B. C.; Burford, D. L. W.; Ho, Y.-P. *J. Chem. Res (S)* **1989**, 386.

(7) Jarrar, A. A. *J. Heterocycl. Chem.* **1978**, *15*, 177.

0022-3263/91/1956-0865$02.50/0