carbamic fluoride, 68986-55-0; fluoro(trifluoromethyl)carbamic fluoride, 68986-54-9; carbonic difluoride, 353-50-4; pentafluoromethanamine, 335-01-3; sodium 2,2,2-trifluoroethoxide, 420-87-1; sodium hexafluoroisopropoxide, 6919-74-0; sodium nonafluoro-*tert*-butoxide, 17526-77-1; potassium nonafluoro-*tert*-butoxide, 29646-16-0; trifluoromethyl hydroperoxide, 16156-36-8; 1,1,1-trifluoro-*N*-(trifluoromethyl)methanamine, 371-77-7; bis(trifluoromethyl)carbamic fluoride, 432-00-8; trifluoromethanethiol, 1493-15-8; bis(trifluoromethyl) disulfide, 372-64-5; trifluoroisocyanatomethane, 460-49-1.

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Ortho Functionalization of Aromatic Amines: Ortho Lithiation of *N*-Pivaloylanilines

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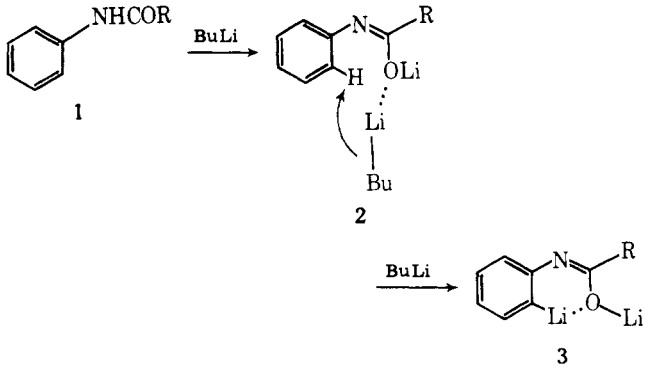
A method is described to convert *N*-pivaloylanilines and toluidines into their *o*-lithio and *o*-(lithiomethyl) derivatives, respectively. These species, in particular those derived from *p*-chloro-, *m*-methoxy-, and *o*-methylaniline, react with a variety of electrophiles (dimethyl disulfide, methyl iodide, DMF, benzaldehyde, trimethylsilyl chloride, acetaldehyde, CO_2) to give ortho-substituted derivatives in very good yield. *N*-Pivaloyl-*m*-anisidine can be functionalized regiospecifically in the 2 position. The pivalamido function is slightly superior to a methoxyl group as an ortho director.

Although electrophilic substitution of anilines, in particular of *N*-acylated derivatives, is feasible,[1,2] the formation of isomers and the marginal yields are synthetically unattractive. More recently a regiospecific ortho alkylation of aromatic amines has been developed based on a Sommelet–Hauser type rearrangement of azasulfonium ylides.[3,4] While the method offers considerable improvement, the reductive removal of the sulfur substituent and the formation of isomers in meta-substituted anilines still present disadvantages. A novel method which permits a specific ortho hydroxyalkylation of secondary anilines and ortho acylation of primary anilines is based on the use of anilinodichloroboranes.[5] While our own work was in progress, Walborsky[6] reported an α addition followed by ortho metalation of phenyl isocyanide. The reaction constitutes, in principle, an ortho metalation of a protected primary aniline but appears to occur only sluggishly relative to other ortho lithiations. We here wish to report on the facile and regioselective ortho lithiation of *N*-pivaloylanilines.

The nitrogen atom in *N,N*-dialkylanilines rates as one of the weakest ortho-directing groups,[7] and lithiation of such substrates can usually be attained only under forcing conditions. The presence of two active hydrogens in primary anilines is a formidable obstacle to nuclear metalation and is presumably the reason for the lack of reports on successful ortho lithiations (cf. ref 6). As part of a systematic search for synthetically useful aniline derivatives as ortho-directing groups, we investigated the suitability of acylated anilines **1**.



1 2 3

Fundamentally it could be assumed that by analogy with other ortho metalations[7] the oxygen (or nitrogen) atom in the deprotonated species **2** should serve as a ligand for a second equivalent of lithiating agent, thus facilitating a regiospecific protophilic attack on the *o*-hydrogen and formation of the dilithio intermediate **3**. It was evident that the nature of R had to be such that no deprotonation of R could occur. Since lithiation of benzanilide occurs exclusively in the position ortho to the carbonyl group,[8] R could not be aryl. Most alkyl groups had to be excluded as well, based on the acidic character of their α protons.[9] The pivaloyl residue (R = C_4H_9-*t*), however, turned out to be ideal, and the desired reaction occurred readily and under relatively mild conditions. This is illustrated (Scheme I) by the facile lithiation of the *p*-chloro derivative

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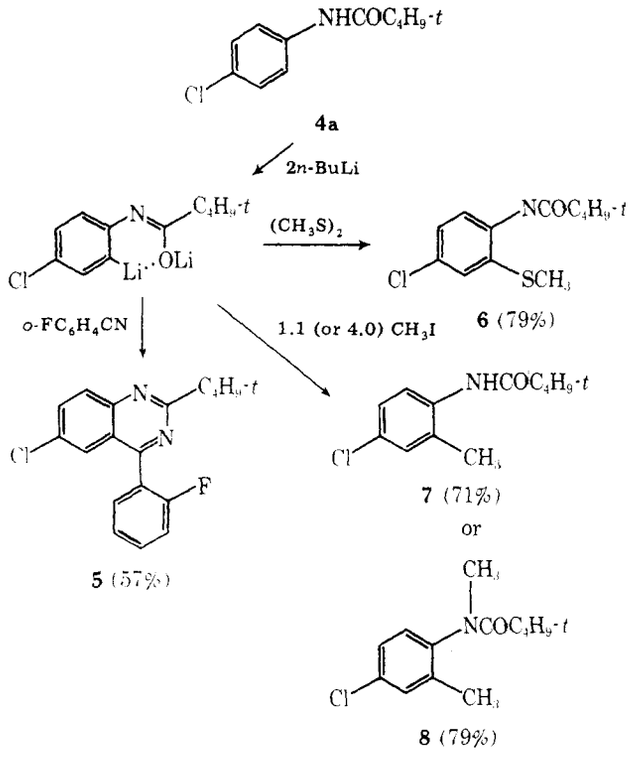
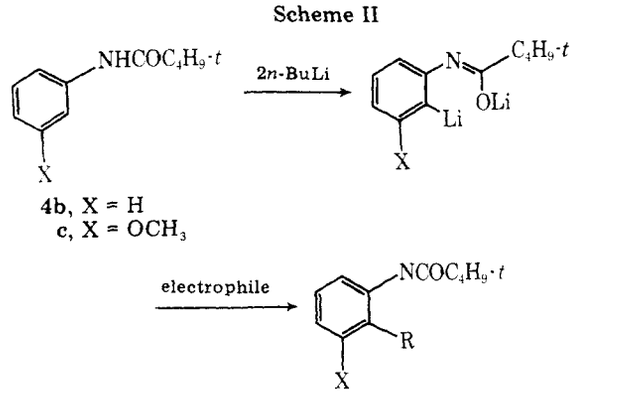
Scheme I



4a with *n*-butyllithium in tetrahydrofuran at 0 °C. Reaction of the dilithio species with dimethyl disulfide results in an almost quantitative formation of the thioether **6** (93% by GC) which can be isolated in 79% yield by crystallization. Alkylation with 1 equiv of methyl iodide occurs selectively at carbon, thus yielding the *o*-tolyl derivative **7**, whereas with an excess of alkylating agent the product of dialkylation **8** can be obtained. Ortho interactions, which are often observed in certain primary products derived from ortho-lithiated species,[7] can be used to advantage as illustrated by the one-step preparation of the quinazoline **5**.

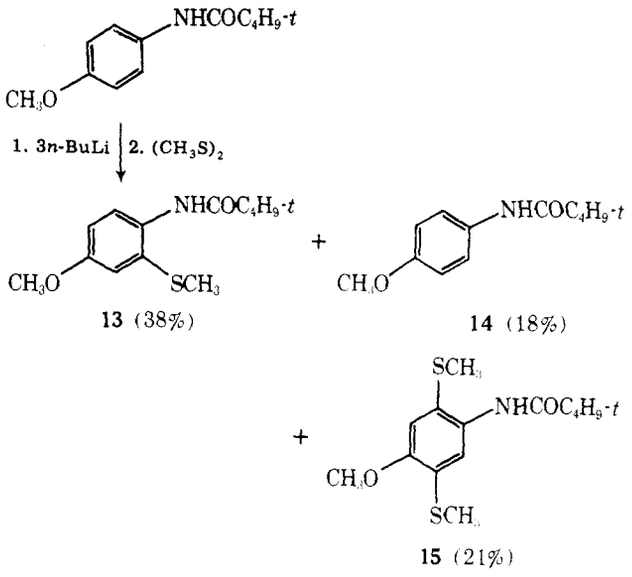
The dilithiation of the unsubstituted derivative **4b** (Scheme II) proceeds, as expected, more slowly relative to **4a**, and a 50% excess of *n*-butyllithium is required to make up for its consumption by the solvent[10] (tetrahydrofuran). Nevertheless, it is possible to generate the dilithio species in an efficient manner as evidenced by the high analytical yield (88% by GC) of the thioether **9**. Metalation of the *m*-methoxy derivative

Scheme II



9, X = H; R = SCH_3; electrophile = $(CH_3S)_2$; 78%
10, X = H; R = CHO; electrophile = DMF; 53%
11, X = OCH_3; R = SCH_3; electrophile = $(CH_3S)_2$; 82%
12, X = OCH_3; R = $CH(OH)C_6H_5$; electrophile = C_6H_5CHO; 79%

Scheme III

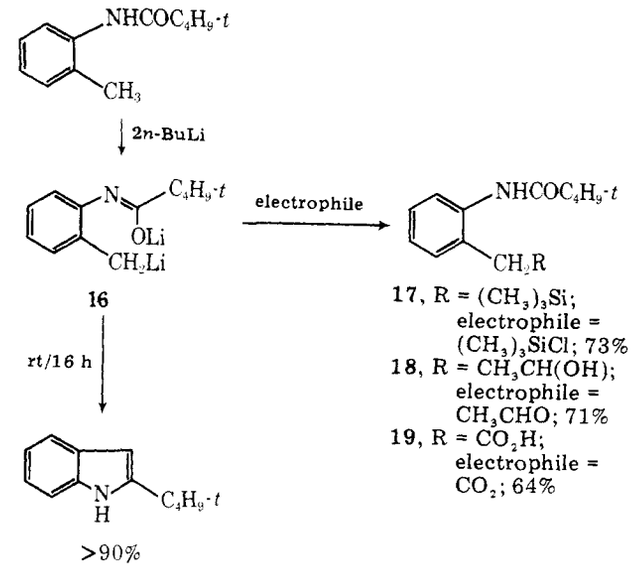


4c is again very rapid, largely because of the combined ortho-directing effects exerted by the pivalamido and the methoxyl group. The lithiation is not only facile but, more importantly, regiospecific as it produces the 1,2,3-trisubstituted derivatives **11** and **12** exclusively. Access to such substitution patterns in aromatic substrates is generally not a trivial problem, and it would appear that the method described provides a viable solution.

Preparatively not very useful is the lithiation of the *p*-anisidine derivative **4d** (Scheme III). In this substrate the ortho-directing effect of the pivalamido and methoxyl groups is competitive as illustrated by the isolation of three different products **13**, **14**, and **15**. The bis(methyl thioether) **15** apparently is the reaction product of a trilithio species with dimethyl disulfide. The 2:1 ratio of **13**–**14** indicates that the pivalamido group is slightly superior to an ether function in terms of its ortho-directing ability. This finding also implies that in comparison to other ortho-directing moieties,[7] the pivalamido group ranks considerably higher than a secondary or tertiary aromatic amine.

Lateral rather than nuclear lithiation, which is generally observed in substrates with a methyl substituent in a position ortho with respect to the directing group,[7] also takes place in *N*-pivaloyl-*o*-toluidine (Scheme IV). In fact, the dianion **16**

Scheme IV



17, R = $(CH_3)_3Si$; electrophile = $(CH_3)_3SiCl$; 73%
18, R = $CH_3CH(OH)$; electrophile = CH_3CHO; 71%
19, R = CO_2H; electrophile = CO_2; 64%

is formed readily and exclusively, and it represents a likely intermediate in the Madelung indole synthesis.[11] Under the mild reaction conditions, however, the dianion can be reacted with a variety of electrophiles as illustrated by the formation of products **17, 18,** and **19.** It is only upon prolonged stirring at room temperature that **16** suffers loss of Li_2O to form 2-*tert*-butylindole[12] in essentially quantitative yield.

The lithiation of *N*-pivaloyl-*o*-toluidine is reminiscent of the deprotonation of *o*-tolyl isocyanide reported to take place under carefully controlled conditions.[13] The reaction has been used to prepare 3-substituted indoles.

In synopsis, lithiation of *N*-pivaloylanilines and toluidines is a facile, practical, and in most cases regiospecific process providing access to a broad variety of ortho-substituted derivatives which in many instances were available only via multistep sequences. The starting materials are readily accessible, and the pivaloyl protecting group can be removed hydrolytically (HCl or Et_3OBF_4/H_2O). The method has considerable synthetic advantages not only in the elaboration of specifically di-, tri-, or tetrasubstituted anilines but also in preparing bicyclic heterocycles (quinazolines, benzoxazines, indolines, indoles) in very short sequences.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as internal standard. The following abbreviations are used: (ex) exchangeable with D_2O; (s) singlet; (d) doublet; (t) triplet; (q) quartet; (m) multiplet.

2-*tert*-Butyl-6-chloro-4(2-fluorophenyl)quinazoline (5). A solution of **4a** (10.6 g, 50 mmol) in 150 mL of THF was cooled in an ice bath under an atmosphere of nitrogen. Then a solution of *n*-BuLi (2.2 m, 50 mL) in hexane was added dropwise. After stirring at 0 °C for 2 h, a solution of *o*-fluorobenzonitrile (6 mL, 55 mmol) in 10 mL of THF was added. The reaction mixture was then stirred for 16 h at 25 °C, quenched with water, diluted with ether, and separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue (16.1 g) was filtered through a column of silica gel using toluene as solvent. Fractions 1–3 (10 g) were crystallized from hexane to give 8.8 g (57%) of **5**: mp 82–84 °C; IR (Nujol) 1615 and 1550 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9 H) and 7.1–8.15 (m, 7 H). Anal. Calcd for $C_{18}H_{16}ClFN$: C, 68.68; H, 5.12; N, 8.89. Found: C, 68.74; H, 5.38; N, 8.84.

4′-Chloro-2,2-dimethyl-2′-thiomethylpropionanilide (6). A solution of **4a** (2.12 g, 10 mmol) in 30 mL of dry THF was cooled in an ice bath under N_2. Then a hexane solution of 2.9 M of *n*-BuLi (8.7 mL, 25 mmol) was added dropwise. After stirring in the ice bath for 2 h, dimethyl disulfide (1.5 mL, ca. 25 mmol) diluted with 2 mL of THF was added. The reaction mixture was then stirred for 2 h at 25 °C, diluted with ether, quenched with water, washed with brine, and dried over $MgSO_4$. After evaporation 2.68 g (93% by GC) of crude **6** were obtained. This product was recrystallized from pentane to give 2.04 g (79%): mp 52–53 °C; NMR ($CDCl_3$) δ 1.38 (s, 9 H), 2.38 (s, 3 H), 7.15–7.45 (m, 2 H), 8.35 (d, J = 9 Hz, 1 H), and 8.6 (s, ex, 1 H); IR (Nujol) 3250, 1691, and 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NOS$: C, 55.91; H, 6.28; N, 5.43. Found: C, 56.11; H, 6.35; N, 5.05.

4′-Chloro-2,2,2′-trimethylpropionanilide (7). A solution of **4a** (2.12 g, 10 mmol) in 30 mL of dry THF was lithiated as described for **6** (8.7 mL, 2.9 M *n*-BuLi). After stirring in the ice bath for 2 h, methyl iodide (1.56 g, 11 mmol) diluted with 3 mL of hexane was added. The solution was then stirred for 1.5 h at 0 °C and for 1 h at 25 °C, diluted with ether, quenched with water and ice, washed with brine, and dried over $MgSO_4$. After evaporation 2.3 g (88% by GC) of crude **7** were obtained. This product was recrystallized from ethyl acetate/hexane to give 1.6 g (71%): mp 118–120 °C; NMR ($CDCl_3$) δ 1.29 (s, 9 H), 2.14 (s, 3 H), and 7.08–7.38 (m, 4 H); IR (Nujol) 3310 and 1636 cm^{-1}. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.20. Found: C, 64.01; H, 7.20; N, 6.19.

4′-Chloro-2,2,2′,*N*-tetramethylpropionanilide (8). Same procedure as described for **7**, but an excess of methyl iodide (2.5 mL, 40 mmol) was used. After workup 2.3 g (93% by GC) of crude **8** was isolated. The product was recrystallized from pentane to give 1.9 g (79%): mp 59–61 °C; NMR ($CDCl_3$) δ 1.10 (s, 9 H), 2.30 (s, 3 H), 3.17 (s, 3 H), and 7.18–7.35 (m, 3 H); IR (Nujol) 1618 cm^{-1}. Anal. Calcd for $C_{13}H_{18}ClNO$: C, 65.17; H, 7.57; N, 5.85. Found: C, 65.23; H, 7.58; N, 5.60.

2,2-Dimethyl-2′-thiomethylpropionanilide (9). A solution of **4b** (1.77 g, 10 mmol) in a mixture of 15 mL of dry THF and 20 mL of dry ether was cooled in an ice bath under N_2. Then a hexane solution of 2.6 M *n*-BuLi (11.6 mL, 30 mmol) was added dropwise. After stirring at 25 °C for 20 h, the suspension was cooled again in an ice bath and dimethyl disulfide (2.2 mL, ca. 37 mmol) was added. The mixture was then stirred for 30 min at 0 °C and for 2 h at 25 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 2.1 g (87% by GC) of crude **9** was obtained. This product was distilled in a Kugelrohr to give 1.75 g (78%): bp 120 °C (0.5 mm); NMR ($CDCl_3$) δ 1.32 (s, 9 H), 2.37 (s, 3 H), 6.90–7.62 (m, 3 H), 8.33–8.51 (m, 2 H), and 8.78 (s, ex, 1 H); IR (CH_2Cl_2) 3350, 1673, and 1570 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.52; H, 7.67; N, 6.27. Found: C, 64.25; H, 7.73; N, 6.45.

2′-Formyl-2,2-dimethylpropionanilide (10). A solution of **4b** (1.77 g, 10 mmol) was lithiated as described for **8** (11.6 mL, 2.6 M *n*-BuLi). After stirring for 20 h at 25 °C, the suspension was cooled again in an ice bath and DMF (5 mL) was added dropwise. The mixture was then stirred for 2 h at 10 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 4.2 g of crude **10** was obtained. This product was chromatographed on silica gel, eluted with methylene chloride/hexane (1:1), and afterwards distilled to give 2.1 g (53%) of **10:** bp 110 °C (0.4 mm); NMR ($CDCl_3$) δ 1.35 (s, 9 H), 7.05–7.70 (m, 3 H), 8.70–8.85 (m, 1 H), and 9.97 (s, 1 H); IR (CH_2Cl_2) 3310, 1673, 1608, and 1582 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.35; N, 6.82. Found: C, 70.28; H, 7.27; N, 7.05.

3′-Methoxy-2,2-dimethylthiomethylpropionanilide (11). A solution of **4c** (2.07 g, 10 mmol) in 30 mL of dry THF was cooled in an ice bath under N_2. Then a hexane solution of 2.6 M *n*-BuLi (9.6 mL, 25 mmol) was added dropwise. After stirring in the ice bath for 2 h, dimethyl disulfide (1.5 mL, ca. 25 mmol) diluted with 2 mL THF was added. The mixture was then stirred for 1 h at 0 °C and for 2 h at 25 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 2.5 g (97%) of crude **11** were obtained. This product was recrystallized from hexane to give 2.08 g (82%): mp 58–60 °C; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 2.27 (s, 3 H), 3.86 (s, 3 H), 6.58–8.25 (m, 3 H), and 9.47 (s, ex, 1 H); IR (liquid) 3350, 1685, and 1590 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.64; H, 7.55; N, 5.53. Found: C, 61.98; H, 7.80; N, 5.35.

2′-(α-Hydroxybenzyl)-3′-methoxy-2,2-dimethylpropionanilide (12). A solution of **4c** (2.07 g, 10 mmol) in 30 mL of dry THF was lithiated as described for **14.** After stirring in the ice bath for 2 h, freshly distilled benzaldehyde (1.6 g, 15 mmol) dissolved in 3 mL of THF was added dropwise. The mixture was then stirred for 40 min at 0 °C and for 1 h at 25 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 3.6 g of crude **12** was obtained. This product was recrystallized from ethyl acetate to give 2.47 g (79%): mp 173–174 °C; NMR (Me_2SO) 1.00 (s, 9 H), 3.60 (s, 3 H), 6.42–7.88 (m, 10 H), and 9.65 (s, ex, 1 H); IR (Nujol) 3255, 1639, 1605, and 1587 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.81; H, 7.40; N, 4.47. Found: C, 72.84; H, 7.43; N, 4.47.

Lithiation of 4′-Methoxy-2,2-dimethylpropionanilide (4d) to Give 13, 14, and 15. A solution of **4d** (2.07 g, 10 mmol) in a mixture of 30 mL of dry THF and 10 mL of dry ether was cooled in an ice bath under N_2. Then a hexane solution of 2.5 M *n*-BuLi (12 mL, 30 mmol) was added dropwise. After stirring at 25 °C for 20 h, the suspension was cooled again in an ice bath and dimethyl disulfide (2.2 mL, ca. 37 mmol) was added. The mixture was then stirred for 1 h at 0 °C and 2 h at 25 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 2.6 g of a mixture of three products was obtained. Separation was possible by preparative TLC (silica gel, ether/hexane 1:2), leading to 0.47 g (18%) of **14,** 0.98 g (38%) of **13,** and 0.54 g (18%) of **15. 11:** mp 142–143 °C; NMR ($CDCl_3$) δ 1.27 (s, 9 H), 2.42 (s, 3 H), 3.87 (s, 3 H), and 6.67–7.55 (m, 4 H); IR (Nujol) 3440 and 1668 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.55; H, 7.68; N, 5.41. **13:** bp 120 °C (0.4 mm); NMR ($CDCl_3$) δ 1.30 (s, 9 H), 2.35 (s, 3 H), 3.73 (s, 3 H), 6.70–7.01 (m, 2 H), 8.18 (d, J = 9.5 Hz, 1 H), and 8.32 (s, ex, 1 H); IR (CH_2Cl_2) 3360 and 1666 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.39; H, 7.63; N= 5/4[/ **[5:** mp 107–108 °C; NMR ($CDCl_3$) δ 1.25 (s, 9 H), 2.30 (s, 3 H), 2.44 (s, 3 H), 6.95 (s, 1 H), 8.33 (s, 1 H), and 8.7 (s, ex, 1 H); IR (CH_2Cl_2) 3352 and 1560 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2S_2$: C, 56.61; H, 7.07; N, 4.68. Found: C, 56.32; H, 7.21; N, 4.57.

2,2-Dimethyl-2′-trimethylsilylmethylpropionanilide (17). A solution of 2,2,2′-trimethylpropionanilide (1.91 g, 10 mmol) in 30 mL of dry THF was cooled in an ice bath under N_2. Then a hexane solu-

tion of 2.5 M *n*-BuLi (10 mL, 25 mmol) was added dropwise. After stirring in the ice bath for 1.5 h, chlorotrimethylsilane (2.5 mL, ca. 20 mmol) was added slowly. The mixture was then stirred for 1 h at 25 °C, diluted with ether, quenched with ice and water, washed with brine, and dried over $MgSO_4$. After evaporation 2.9 g (80% by GC) of crude **17** was obtained. The product was first separated by preparative TLC (silica gel, chloroform/ethyl acetate 9:1 as solvent) and then crystallized from pentane to give 1.9 g (73%): mp 79–81 °C; NMR ($CDCl_3$) δ 0.0 (s, 9 H), 1.30 (s, 9 H), 2.02 (s, 2 H), and 6.98–7.91 (m, 5 H); IR (Nujol) 3255, 1639, 1605, and 1587 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NOSi$: C, 68.38; H, 9.56; N, 5.31. Found: C, 68.17; H, 9.65; N, 5.21.

2′-(β-Hydroxypropyl)-2,2-dimethylpropionanilide (18). A solution of 2,2,2′-trimethylpropionanilide (1.91 g, 10 mmol) in 30 mL of dry THF was lithiated as described for **17** (10 mL, 2.5 M *n*-BuLi). After stirring in the ice bath for 1.5 h, the solution was cooled to −70 °C and dry acetaldehyde (1.6 mL, ca. 30 mmol) was added slowly. The solution was then stirred for 10 min at −70 °C and 2 h at 0 °C, diluted with ether, quenched with water and ice, washed with brine, and dried over $MgSO_4$. After evaporation 3.8 g of crude **18** was obtained. This product was recrystallized from ethyl acetate/pentane to give 1.67 g (71%): mp 104–105 °C; NMR (Me_2SO) δ 1.08–1.27 (m, 12 H), 2.58–2.70 (m, 2 H), 3.68–4.18 (m, 1 H), 5.58 (d, ex, 1 H), 7.02–7.75 (m, 4 H), and 9.65 (s, ex, 1 H); IR (Nujol) 3360, 3250, and 1656 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.44; H, 9.00; N, 5.94. Found: C, 71.48; H, 8.94; N, 5.92.

2-Carboxy-2,2-dimethylpropionanilide (19). A solution of 2,2,2′-trimethylpropionanilide (1.91 g, 10 mmol) in 30 mL of dry THF was lithiated as described for **17** (10 mL, 2.5 M *n*-BuLi). In a second flask 30 mL of dry THF was cooled to −70 °C under nitrogen together with 5 g of powdered dry ice. The solution with the lithiated species was now slowly pumped (small steel tube through serum caps, nitrogen pressure) into the flask containing the CO_2. The reaction mixture was then stirred for 10 min at −70 °C, slowly warmed up to 0 °C, diluted with ether, quenched with ice, and extracted several times with 1 N NaOH. The basic solution was acidified with 2 N HCl and extracted with ether and the organic phase was dried over $MgSO_4$. After evaporation 1.7 g (73%) of crude **19** was obtained. This product was recrystallized from ethyl acetate to give 1.5 g (64%): NMR (Me_2SO) δ 1.60 (s, 9 H), 3.62 (s, 2 H), 7.05–7.40 (m, 4 H), 8.98 (s, ex, 1 H), and 12.5 (s, ex, 1 H); IR (Nujol) 3300, 1696, and 1640 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.38; N, 5.80.

Preparation of Starting Materials. The general procedure involved reaction of the aniline and pivaloyl chloride (1:1) in a two-phase system of methylene chloride–aqueous sodium carbonate for 4–16 h at room temperature: **4a,** mp 145 °C (96%); **4b,** mp 118–120 °C (97%); **4c,** mp 130–131 °C (80%); **4d,** mp 124–125 °C (88%); 2,2,2′-trimethylpropionanilide, mp 109–111 °C (85%).

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Registry No.—**4a,** 65854-91-3; **4b,** 6625-74-7; **4c,** 56619-93-3; **4d,** 56619-94-4; **5,** 68965-75-3; **6,** 68965-76-4; **7,** 68965-77-5; **8,** 68965-78-6; **9,** 68965-79-7; **10,** 6141-21-5; **11,** 68965-80-0; **12,** 68965-81-1; **13,** 68965-82-2; **14,** 68965-83-3; **15,** 68965-84-4; **17,** 68975-44-0; **18,** 68965-85-5; **19,** 68965-86-6; *o*-fluorobenzonitrile, 394-47-8; dimethyl disulfide, 624-92-0; 2,2,2′-trimethylpropionanilide-, 61495-04-3; chlorotrimethylsilane, 75-77-4; acetaldehyde, 75-07-0; pivaloyl chloride, 3282-30-2; 4-chlorobenzenamine, 106-47-8; benzenamine, 62-53-3; 3-methoxybenzenamine, 536-90-3; 4-methoxybenzenamine, 104-94-9; 2-methylbenzenamine, 95-53-4; methyl iodide, 74-88-4; DMF, 68-12-2; benzaldehyde, 100-52-7.

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Transmission of Substituent Effects in Heterocyclic Systems by Carbon-13 Nuclear Magnetic Resonance. Benzothiazoles

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The carbon-13 NMR spectra of 57 benzothiazoles including 6-substituted 2-aminobenzothiazoles (**1**), 6-substituted 2-methylbenzothiazoles (**2**), 6-substituted benzothiazoles (**3**), 5-substituted 2-methylbenzothiazoles (**4**) and 2-substituted benzothiazoles (**5**) were determined in Me_2SO-d_6. The chemical shift assignments were made based upon the ones previously reported for benzothiazole, 2-aminobenzothiazole, and 2-methylbenzothiazole, chemical shift and signal intensity arguments, and by interpretation of their proton-coupled spectra. The chemical shift data for carbon 2 and carbon 9 for series **1–3** and carbon 2 and carbon 8 for series **4** gave good correlations with simple Hammett constants, and slightly better correlations with a linear combination of σ_m and σ_p, Swain–Lupton, and Taft–DSP treatments. Results from the dual parameter approaches indicate that resonance effects are primarily responsible for the substituent effect on chemical shifts at the carbons in question. The data also indicate that transmission of substituent effects by the sulfur atom is limited and that the primary path of transmission of substituent effects to carbon 2 is through nitrogen. The data from series **3** and **5** suggest that transmission of substituent effects by substituents on carbon 2 to carbon 6 is approximately one-third less effective than transmission by substituents on carbon 6 to carbon 2.

Carbon-13 NMR is recognized as a useful tool to obtain information regarding the electronic environment of carbon atoms of interest. In spite of the fact that quantitative correlations between carbon-13 chemical shifts and calculated electronic densities frequently cannot be obtained, carbon-13 shifts do, however, provide qualitative information about charge densities at carbon atoms of similar hybridization.[1] Carbon-13 NMR spectroscopy has been used extensively for

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