Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2893–2897

TETRAHEDRON

An unusual behaviour of *N*-(*tert*-butoxycarbonyl)- and *N*-pivaloyl-(methylthio)anilines in metallation reactions☆

Maria Grazia Cabiddu, Salvatore Cabiddu,* Enzo Cadoni, Stefania De Montis, Claudia Fattuoni* and Stefana Melis

Dipartimento di Scienze Chimiche, Cittadella Universitaria di Monserrato, S.S. 554 Bivio per Sestu, I-09042 Monserrato (CA), Italy

Received 28 November 2002; revised 7 February 2003; accepted 27 February 2003

Abstract—The metallation reaction of *N*-Boc-and *N*-Piv-(methylthio)anilines are here described. The results show that *N*-Boc derivatives are metallated only by superbases to give products substituted at the thiomethylic group. *N*-Piv derivatives show a different behaviour: *ortho*-derivative is metallated by both butyllithium and superbase at the thiomethylic carbon atom, while *para*-derivative is metallated in *ortho* to the *N*-Piv group by butyllithium and at the thiomethylic carbon atom by superbase. The *meta*-derivative is metallated only by superbase at the thiomethylic carbon atom.

Anilines bearing thiomethylic groups are useful building blocks to synthesise biologically active molecules. In a previous paper[2] we showed that *N*,*N*-dimethyl-4-(methylthio)aniline reacts with butyllithium to give mixtures of products substituted at the arylic and the thiomethylic hydrogen, while with superbases gives only the product derived from the substitution of the thiomethylic hydrogen. On the other side, *ortho* and *meta* isomers are metallated only at the thiomethylic position with both reagents.

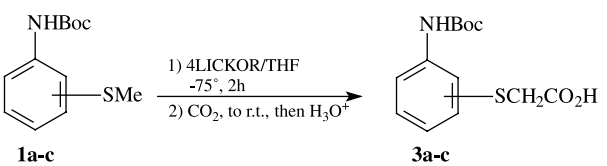
Stanetty and co-workers reported the direct *ortho*-lithiation of *N*-Boc-anilines, analyzing the best reaction conditions (organolithium, solvent, temperature, reaction time) to obtain the highest yield.[3] Other papers[4–8] described the *N*-Boc group as a powerful *ortho*-directing group in the metallation of arenes bearing various substituents.

In this work we examined the reactivity of *N*-Boc protected anilines bearing a methylthio group in the *ortho*, *meta*, or *para* position to test their relative directing power in the annular metallation reaction, with the aim of further functionalisation of these substrates after removal of the Boc group.

All starting compounds were reacted with various alkyllithium (butyllithium, *tert*-butyllithium): all metallated compounds were quenched with carbon dioxide and analysed by spectroscopic methods.

The metallation reactions were performed at various temperatures (−60, −40, −20, −10, 0°C) at different metallating reagent concentrations (2, 3, 4, 8 M equiv. of organometallic reagent), with reaction times ranging from 30 min to 8 h. Contrary to our expectations, the reactions performed on **1a–c** gave only the starting material and a small quantity (ca. 5%) of unidentifiable products. Then we changed the metallating reagent employing the superbasic mixture LICKOR (butyllithium and potassium *tert*-butoxide). In this way (Scheme 1), all isomers afforded products substituted at the thiomethylic position (**3a–c**, respectively) with a yield of 70, 56, and 75%. The best results were obtained using 4 M equiv. of LICKOR. Every attempt to bimetallate the same substrates failed even using 6–8 M equiv. of metallating reagent.

In order to substitute one arylic hydrogen we tested the pivaloyl protecting group because NHPiv is reported to act



1a-c **3a-c**

Entry	Product	Yield (%)
o-isomer **1a**	*o*-isomer **3a**	70
m-isomer **1b**	*m*-isomer **3b**	56
p-isomer **1c**	*p*-isomer **3c**	75

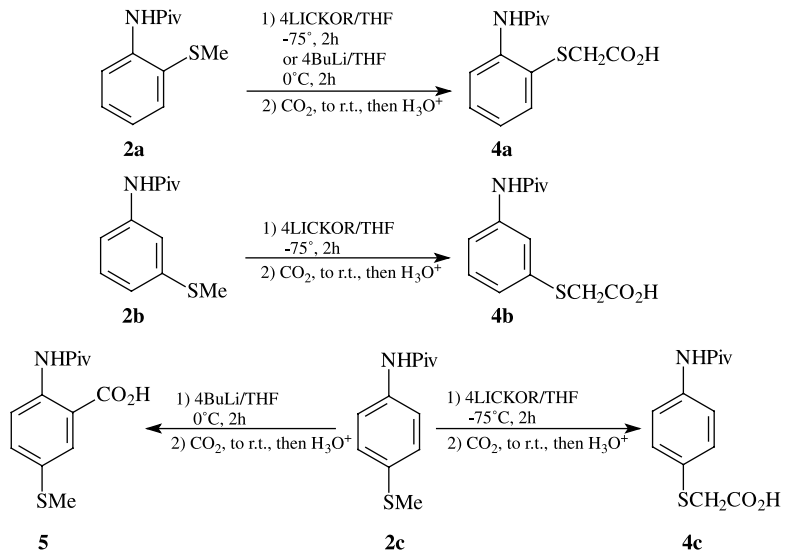
Scheme 1.

☆ See Ref. 1.

Keywords: metallation; lithiation; thioethers; anilines.

* Corresponding authors. Tel.: +39-70-6754387; fax: +39-70-6754388; e-mail: scabiddu@unica.it

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00347-8



Entry	Organo-metallic	Product	Yield (%)	Entry	Organo-metallic	Product	Yield (%)
o-isomer **2a**	BuLi	*o*-isomer **4a**	55	*m*-isomer **2b**	LICKOR	*m*-isomer **4b**	63
o-isomer **2a**	LICKOR	*o*-isomer **4a**	68	*p*-isomer **2c**	BuLi	*p*-isomer **5**	65
m-isomer **2b**	BuLi	--------		*p*-isomer **2c**	LICKOR	*p*-isomer **4c**	65

Scheme 2.

as a more powerful *ortho*-directing group in metallation reactions.[9,10] The results (Scheme 2) showed that the *ortho* isomer (**2a**) gives products deriving from the substitution of one thiomethylic hydrogen with both organolithiums and superbases. On the contrary, the *para* isomer (**2c**) is metallated in *ortho* to the NHPiv group with butyllithium, while the superbase leads to the substitution of one thiomethylic hydrogen. Even with these compounds the increase in the amount of organolithium does not significantly affect the yield. Unexpectedly, **2b** afforded only starting material when treated with butyllithium, while using the superbase we obtained the product **4b** derived from a thiomethylic substitution.

In conclusion, examining the results it may be deduced that the *N*-Boc interferes with the thiomethylic group inhibiting the coordination and then the metallation cannot occur. Only superbases are able to act on these substrates abstracting the most acidic hydrogens, i.e. the thiomethylic ones. In support of this hypothesis it can be noticed that the *N*-Piv group, more effective than *N*-Boc to promote coordinative processes, allows reactions not only with superbase but even with organolithium. Moreover the metallating reagents show different regioselectivity, as expected: with **2c** the organolithium selectively metallates the position *ortho* to the *N*-Piv, due to its stronger coordinating power than the thiomethyl group; on the other side, the superbase selectively metallates the more acidic thiomethylic group. The *ortho* isomer **2a**, on the contrary, is lithiated at the thiomethylic carbon even with the organolithiums. This result can be accounted for by the stabilisation of the thiomethyl carbanion by the adjacent *N*-Piv group (Fig. 1).[11]

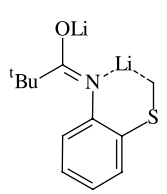
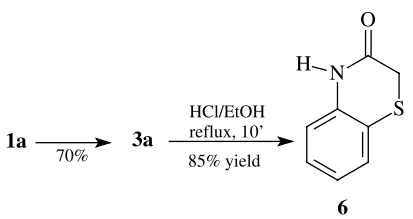


Figure 1.

It is remarkable that all reactions require a great concentration of metallating reagent: this phenomenon can be explained in terms of competitive complexation processes, due to the presence of many coordinating heteroatoms.

Moreover **1a**, through its derivative **3a**, shows to be a useful precursor of 1,4-benzothiazines, as proved by the attainment of compound **6** (Scheme 3).



Scheme 3.

1. Experimental

1.1. General

^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin–Elmer 1310 grating

spectrophotometer. The GC–MS analyses were performed with a Hewlett–Packard 5989A GC–MS system with HP 5890 GC fitted with a capillary column (50 m×0.2 mm) packed with DH 50.2 Petrocol (0.50 m film thickness). All flash chromatography was on silica G60 (Merck) columns. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser. Melting points were obtained on a Kofler hot stage microscope and are uncorrected.

1.2. Materials

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane and *tert*-butyllithium in pentane were obtained from Aldrich Chemical Company and were analysed by the Gilman double titration method before use.[12] 2-(Methylthio)-3-(methylthio) and 4-(methylthio)aniline were purchased (Aldrich).

1.2.1. *N*-(*tert*-Butoxycarbonyl)-2-(methylthio)benzenamine (1a). A solution of 2-(methylthio)benzenamine (5 g, 36 mmol) in dry tetrahydrofuran (50 mL) was blanketed with argon and then treated dropwise at room temperature with a solution of *tert*-butylcarbonate (8.6 g, 40 mmol) in dry tetrahydrofuran (20 mL). When the addition was complete the mixture was stirred for ca. 15 h at 60°C, cooled, diluted with diethyl ether (25 mL), washed with 5% hydrochloric acid and then with aqueous sodium carbonate. The ethereal solution was dried (Na_2SO_4) and concentrated. The residue was flash-chromatographed on a silica gel column using 20:1 hexane/ethyl acetate to give the title compound **1a** (5.77 g, 67%) as a yellow viscous oil;[3] [Found: C, 60.15; H, 7.11; N, 5.78; S, 13.29. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85; S, 13.40%]; ν_{max} (neat) 3370 (NH), 1730 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.51 (9H, s, CCH_3), 2.33 (3H, s, SCH_3), 6.95 (1H, t, *J*=7.3 Hz, Ph), 7.24 (1H, t, *J*=7.4 Hz, Ph), 7.43 (1H, d, *J*=7.8 Hz, Ph), 7.61 (1H, s, N*H*, D_2O exchangeable), 8.11 (1H, d, *J*=8.3 Hz, Ph); δ_c (75.4 MHz, $CDCl_3$) 18.9, 28.2, 80.4, 118.7, 122.9, 124.0, 128.8, 133.1, 138.9, 152.6; *m/z* (EI) 239 (20, M^+), 183 (51), 166 (10), 139 (53), 124 (37), 106 (12), 94 (11), 57 (100), 41 (47%).

Analogously from 3-(methylthio)- and 4-(methylthio)-benzenamine were prepared.

1.2.2. *N*-(*tert*-Butoxycarbonyl)-3-(methylthio)benzenamine (1b). The residue was crystallised from aqueous ethanol to give the title compound **1b** (5.85 g, 68%) as a white solid, mp 74–76°C; [Found: C, 60.11; H, 7.10; N, 5.80; S, 13.31. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85; S, 13.40%]; ν_{max} (nujol) 3335 (NH), 1710 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.51 (9H, s, CCH_3), 2.47 (3H, s, SCH_3), 6.91 (1H, d, *J*=7.8 Hz, Ph), 7.06 (1H, d, *J*=7.5 Hz, Ph), 7.18 (1H, t, *J*=7.8 Hz, Ph), 7.26 (1H, s, Ph), 7.36 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, $CDCl_3$) 15.5, 28.2, 80.5, 115.0, 115.9, 120.8, 129.1, 138.7, 139.3, 152.4; *m/z* (EI) 239 (24, M^+), 183 (58), 166 (7), 165 (7), 139 (24), 106 (32), 94 (3), 57 (100), 41 (37%).

1.2.3. *N*-(*tert*-Butoxycarbonyl)-4-(methylthio)benzenamine (1c). The residue was crystallised from aqueous ethanol to give the title compound **1c** (4.31 g, 50%) as pale yellow crystals, mp 109–110°C; [Found: C, 60.27; H, 7.09; N, 5.88; S, 13.25. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85; S, 13.40%]; ν_{max} ($CHCl_3$,) 3450 (NH), 1720 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.42 (9H, s, CCH_3), 2.35 (3H, s, SCH_3), 6.60 (1H, s, N*H*, D_2O exchangeable), 7.12 (2H, d, *J*=8.5 Hz, Ph), 7.21 (2H, d, *J*=8.5 Hz, Ph); δ_c (75.4 MHz, $CDCl_3$) 17.0, 28.2, 80.5, 119.1, 128.4, 131.7, 136.1, 152.5; *m/z* (EI) 239 (5, M^+), 183 (36), 165 (8), 139 (18), 124 (26), 106 (3), 96 (5), 57 (100), 41 (69%).

1.2.4. 2,2-Dimethyl-*N*-[(2-methylthio)phenyl]propanamide (2a). To an ice-cooled solution of 2-(methylthio)-benzenamine (10 g, 72 mmol) and triethylamine (11.8 g, 117 mmol) in dry tetrahydrofuran (100 mL) was added dropwise under nitrogen a solution of 2,2-dimethylpropanoyl chloride (22.7 g, 188 mmol). The resulting mixture was stirred at room temperature for 4 h, then the solvent was removed in vacuo. The residue was diluted with dichloromethane and washed with 10% aqueous sodium hydroxide, water and dried (Na_2SO_4). After the solvent was removed, the residue was flash-chromatographed on silica gel column with hexane/diethyl ether (6:1) as eluent to give the title compound **2a** (11.09 g, 69%) which was crystallised from hexane as pale yellow crystals, mp 40–44°C (lit.[9] bp 85–90°C/0.005 mm Hg) [Found: C, 64.44; H, 7.61; N, 6.18; S, 14.21. $C_{12}H_{17}NOS$ requires C, 64.53; H, 7.67; N, 6.25; S, 14.36%]; ν_{max} ($CHCl_3$,) 3360 (NH), 1695 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.35 (9H, s, CCH_3), 2.35 (3H, s, SCH_3), 7.02 (1H, t, *J*=7.5 Hz, Ph), 7.27 (1H, t, *J*=7.8 Hz, Ph), 7.45 (1H, d, *J*=7.6 Hz, Ph), 8.37 (1H, d, *J*=8.4 Hz, Ph), 8.72 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, $CDCl_3$) 18.6, 27.4, 39.9, 120.1, 123.8, 125.0, 128.7, 132.8, 138.4, 176.3; *m/z* (EI) 223 (24, M^+), 176 (83), 166 (7), 139 (30), 124 (37), 106 (9), 94 (7), 80 (8), 69 (4), 65 (8), 57 (100), 41 (37%).

In the same manner, starting from 3-(methylthio)- and 4-(methylthio)benzenamine, were prepared:

1.2.5. 2,2-Dimethyl-*N*-[(3-methylthio)phenyl]propanamide (2b). The residue was crystallised from aqueous ethanol to give the title compound **2b** (7.86 g, 71%) as a white solid, mp 134–136°C; [Found: C, 64.58; H, 7.71; N, 6.21; S, 14.27. $C_{12}H_{17}NOS$ requires C, 64.53; H, 7.67; N, 6.25; S, 14.36%]; ν_{max} (Nujol,) 3280 (NH), 1645 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.31 (9H, s, CCH_3), 2.48 (3H, s, SCH_3), 6.98 (1H, m, Ph), 7.20 (2H, m, Ph), 7.38 (1H, s, N*H*, D_2O exchangeable), 7.60 (1H, s, Ph); δ_c (75.4 MHz, $CDCl_3$) 15.6, 27.5, 39.6, 116.4, 117.5, 122.1, 129.1, 138.5, 139.5, 176.7; *m/z* (EI) 223 (12, M^+), 139 (8), 123 (2), 106 (12), 85 (4), 77 (2), 57 (100), 41 (38%).

1.2.6. 2,2-Dimethyl-*N*-[(4-methylthio)phenyl]propanamide (2c). The residue was crystallised from aqueous ethanol to give the title compound **2c** (13.50 g, 84%) as a white solid, mp 143–145°C; [Found: C, 64.41; H, 7.60; N, 6.19; S, 14.24. $C_{12}H_{17}NOS$ requires C, 64.53; H, 7.67; N, 6.25; S, 14.36%]; ν_{max} (Nujol,) 3290 (NH), 1650 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.31 (9H, s, CCH_3), 2.46 (3H, s, SCH_3), 7.23 (2H, d, *J*=8.2 Hz, Ph), 7.35 (1H, s, N*H*, D_2O exchangeable), 7.47 (2H, d, *J*=8.2 Hz, Ph); δ_c (75.4 MHz, $CDCl_3$) 16.7, 27.5, 39.5, 120.6, 127.9, 133.3, 135.6, 176.5; *m/z* (EI) 223 (51, M^+), 180 (2), 165 (2), 139 (30), 124 (31), 111 (2), 96 (3), 85 (5), 69 (3), 65 (2), 57 (100), 41 (25%).

1.3. General procedure for metallation with superbases

To a vigorously stirred solution of potassium *tert*-butoxide (2.24 g, 20 mmol) and anhydrous tetrahydrofuran (25 mL) a 1.4 M solution of butyllithium in hexane (14.3 mL, 20 mmol) was added under argon at −75°C. After 15 min a solution of the starting material (5 mmol) in anhydrous tetrahydrofuran (25 mL) was added and stirring was continued for 2 h at −75°C. The mixture was then poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous $NaHCO_3$ (10 mL) and then with diethyl ether (20 mL). The alkali layer was separated, washed with diethyl ether (3×10 mL) and then acidified with 10% aqueous cold hydrochloric acid, extracted with $CHCl_3$ (3×10 mL), dried (Na_2SO_4) and concentrated.

In this manner starting from **1a–c** and **2a–c** the following compounds were obtained:

1.3.1. 2-({2-[(*tert*-Butoxycarbonyl)amino]phenyl}thio)-acetic acid (3a). The residue was crystallised from aqueous ethanol to give the title compound **3a** (0.99 g, 70%) as pale brown crystals, mp 112–114°C; [Found: C, 55.04; H, 5.98; N, 4.90; S, 11.21. $C_{13}H_{17}NO_4S$ requires C, 55.11; H, 6.05; N, 4.94; S, 11.32%]; ν_{max} ($CHCl_3$) 3500 (NH), 3370 (OH), 1720 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.53 (9H, s, CC*H*$_3$), 3.52 (2H, s, SC*H*$_2$), 6.98 (1H, t, *J*=7.5 Hz, Ph), 7.34 (1H, t, *J*=7.2 Hz, Ph), 7.54 (1H, d, *J*=7.8 Hz, Ph), 7.98 (1H, s, N*H*, D_2O exchangeable), 8.14 (1H, d, *J*=8.4 Hz, Ph); δ_c (75.4 MHz, $CDCl_3$) 28.3, 38.5, 80.9, 119.1, 120.3, 123.1, 130.8, 136.1, 140.5, 152.8, 174.9; *m*/*z* (EI) 283 (12, M^+), 227 (21), 209 (12), 183 (16), 165 (16), 150 (9), 136 (34), 124 (26), 93 (47), 69 (25), 57 (100), 41 (80%).

1.3.2. 2-({3-[(*tert*-Butoxycarbonyl)amino]phenyl}thio)-acetic acid (3b). The residue was crystallised from aqueous ethanol to give the title compound **3b** (0.79 g, 56%) as a pale brown solid, mp 122–124°C; [Found C, 55.02; H, 6.00; N, 4.87; S, 11.19. $C_{13}H_{17}NO_4S$ requires C, 55.11; H, 6.05; N, 4.94; S, 11.32%]; ν_{max} ($CHCl_3$) 3440 (NH), 3300 (OH), 1720 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.52 (9H, s, CC*H*$_3$), 3.67 (2H, s, SC*H*$_2$), 7.06 (1H, m, Ph), 7.21 (2H, d, *J*=5.4 Hz, Ph), 7.26 (1H, s, Ph), 7.43 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, DMSO-d_6) 28.1, 35.1, 79.2, 115.8, 117.3, 121.3, 129.3, 136.0, 140.1, 152.7, 170.4; *m*/*z* (EI) 283 (20, M^+), 227 (30), 224 (17), 183 (97), 166 (7), 164 (8), 150 (26), 138 (48), 124 (8), 109 (8), 94 (56), 80 (32), 65 (20), 57 (100), 41 (94%).

1.3.3. 2-({4-[(*tert*-Butoxycarbonyl)amino]phenyl}thio)-acetic acid (3c). The residue was crystallised from aqueous ethanol to give the title compound **3b** (1.05 g, 75%) as a white solid, mp 153–155°C; [Found C, 55.05; H, 5.99; N, 4.85; S, 11.23. $C_{13}H_{17}NO_4S$ requires C, 55.11; H, 6.05; N 4.94; S, 11.32%]; ν_{max} (Nujol) 3370 (NH), 2720 (OH), 1700 cm^{-1} (CO); δ_H (300 MHz, DMSO-d_6): 1.47 (9H, s, CC*H*$_3$), 3.65 (2H, s, SC*H*$_2$), 7.28 (2H, d, *J*=9.0 Hz, Ph), 7.40 (2H, d, *J*=9.0 Hz, Ph), 9.39 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, DMSO-d_6) 28.4, 36.8, 79.7, 119.1, 127.7, 130.7, 138.7, 153.1, 171.2; *m*/*z* (EI) 283 (6, M^+), 227 (63), 209 (2), 183 (12), 168 (8), 164 (6), 136 (5), 124 (40), 108 (10), 96 (6), 69 (4), 57 (100), 41 (45%).

1.3.4. 2-({2-[(2,2-Dimethylpropanoyl)amino]phenyl}-thio)acetic acid (4a). The residue was crystallised from aqueous ethanol to give the title compound **4a** (0.91 g, 68%) as a white solid, mp 117–121°C; [Found C, 58.31; H, 6.34; N, 5.18; S, 11.87. $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N, 5.24; S, 11.99%]; ν_{max} ($CHCl_3$) 3370 (NH), 3060 (OH), 1710 and 1680 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.33 (9H, s, CC*H*$_3$), 3.56 (2H, s, SC*H*$_2$), 7.05 (1H, t, *J*=7.8 Hz, Ph), 7.34 (1H, t, *J*=7.8 Hz, Ph), 7.56 (1H, d, *J*=7.8 Hz, Ph), 8.32 (1H, d, *J*=8.1 Hz, Ph), 9.13 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, $CDCl_3$) 27.5, 38.8, 40.2, 121.2, 121.9, 124.5, 130.7, 135.9, 140.2, 173.7, 177.2; *m*/*z* (EI) 267 (10, M^+), 176 (51), 165 (18), 136 (16), 124 (19), 109 (5), 93 (26), 57 (100), 41 (39%).

1.3.5. 2-({3-[(2,2-Dimethylpropanoyl)amino]phenyl}-thio)acetic acid (4b). The residue was crystallised from aqueous ethanol to give the title compound **4b** (0.84 g, 63%) as white crystals, mp 105–107°C; [Found C, 58.29; H, 6.36; N, 5.15; S, 11.84. $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N, 5.24; S, 11.99%]; ν_{max} ($CHCl_3$) 3250 (NH), 2740 (OH), 1730 and 1660 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.25 (9H, s, CC*H*$_3$), 3.61 (2H, s, SC*H*$_2$), 7.08 (1H, d, *J*=7.8 Hz, Ph), 7.16 (1H, t, *J*=7.8 Hz, Ph), 7.31 (1H, d, *J*=6.6 Hz, Ph), 7.58 (1H, s, Ph), 8.34 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, $CDCl_3$) 28.1, 36.9, 40.2, 119.7, 122.1, 126.2, 130.0, 136.2, 139.0, 174.3, 178.2; *m*/*z* (EI) 267 (35, M^+,), 223 (61), 183 (23), 164 (4), 138 (12), 108 (4), 94 (6), 57 (100), 41 (31%).

1.3.6. 2-({4-[(2,2-Dimethylpropanoyl)amino]phenyl}-thio)acetic acid (4c). The residue was crystallised from aqueous ethanol to give the title compound **4c** (0.87 g, 65%) as yellow crystals, mp 165–167°C; [Found C, 58.33; H, 6.31; N, 5.18; S, 11.82. $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N, 5.24; S, 11.99%]; ν_{max} (Nujol) 3320 (NH), 2640 (OH), 1730 and 1620 cm^{-1} (CO); δ_H (300 MHz, DMSO-d_6) 1.21 (9H, s, CC*H*$_3$), 3.69 (2H, s, SC*H*$_2$), 7.32 (2H, d, *J*=9.0 Hz, Ph), 7.61 (2H, d, *J*=9.0 Hz, Ph), 9.22 (1H, s, N*H*, D_2O exchangeable); δ_c (75.4 MHz, DMSO-d_6) 27.3, 36.4, 40.4, 120.9, 128.8, 129.8, 138.3, 170.8, 176.6; *m*/*z* (EI) 267 (31, M^+), 183 (10), 165 (2), 150 (9), 124 (20), 108 (6), 91 (2), 57 (100), 41 (38%).

1.4. General procedure for metallation with organolithium compounds

A vigorously stirred solution of starting material (5 mmol) in anhydrous tetrahydrofuran (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (14.3 mL, 20 mmol) at 0°C under argon. After 2 h, the mixture was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate (10 mL) and then with diethyl ether (20 mL). The alkali layer was separated, washed with diethyl ether (3×10 mL), and then acidified with cold concentrated hydrochloric acid, extracted with diethyl ether (3×10 mL), dried (Na_2SO_4), and concentrated.

1a–c afforded only the starting material. The same results were obtained performing the reaction at −60, −40, −20, −10°C. In the case of **2a** the reaction, performed at 0°C, gave the products **4a** in 55% yield. **2b** afforded only the

starting material. In the case of **2c** the following product was obtained.

1.4.1. 2-[(2,2-Dimethylpropanoyl)amino]-5-(methylthio)benzoic acid (5). The residue was crystallised from aqueous ethanol to give the title compound **5** (0.87 g, 65%) as pale brown crystals, mp 149–150°C; [Found C, 58.30; H, 6.33; N, 5.16; S, 11.85. $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N, 5.24; S, 11.99%]; ν_{max} ($CHCl_3$) 3510 (NH), 3320 and 3220 (OH) 1715 and 1670 cm^{-1} (CO); δ_H (300 MHz, $CDCl_3$) 1.37 (9H, s, C–CH_3), 2.51 (3H, s, SCH_3), 7.51 (1H, dd, J=8.7, 2.4 Hz, Ph), 8.04 (1H, d, J=2.1 Hz, Ph), 8.75 (1H, d, J=9.0 Hz, Ph), 10.25 (1H, s, OH, D_2O exchangeable), 11.13 (1H, s, NH, D_2O exchangeable); δ_c (75.4 MHz, $CDCl_3$); 16.7, 27.5, 40.4, 115.0, 121.3, 130.2, 132.3, 134.4, 139.8, 172.1, 178.2; *m/z* (EI) 267 (70, M^+), 192 (12), 183 (71), 165 (56), 150 (8), 122 (10), 91 (8), 69 (6), 57 (100), 41 (68%).

The same results were obtained performing the reactions with 6 or 8 M equiv. of organolithium.

1.4.2. 2*H*-1,4-Benzothiazin-3(4*H*)-one (6). A solution of **3a** (1 g, 3.5 mmol) in ethanol (15 mL) was treated with a solution of 10% hydrochloric acid in ethanol (3 mL). The resulting mixture was heated at reflux for 10 min and the solvent was then removed in vacuo to afford the crude product which was crystallised from aqueous ethanol to give the title compound **6** (0.50 g, 86%) as pale brown needles, mp 178–179°C (lit.[13] mp 181–181.5°C). The compound **6** is identical to the commercial product (Aldrich).

Acknowledgements

Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, The University of Cagliari (National Project 'Stereoselezione in Sintesi Organica, Metodologie ad Applicazioni') and C.N.R. (Italy) is gratefully acknowledged.

References

1. Metallation reactions: part XXXII: for part XXXI, see: Cabiddu, S.; Cadoni, E.; Ianni, A.; Gelli, G.; Melis, S.; Bernard, A.; Cabiddu, M. G.; De Montis, S.; Fattuoni, C. *Eur. J. Org. Chem.* **2002**, 3393–3401.
2. Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Cannas, R.; De Montis, S.; Fattuoni, C.; Melis, S. *J. Organomet. Chem.* **2001**, *620*, 263–275.
3. Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833–6837, and references cited therein.
4. Takagishi, S.; Katsoulos, G.; Schlosser, M. *Synlett* **1992**, 360–362.
5. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801.
6. Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 5505–5508.
7. Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463–5466.
8. Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523–1526.
9. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133–1136.
10. Mulhern, T. A.; Davis, M.; Krikke, J. J.; Thomas, J. A. *J. Org. Chem.* **1993**, *58*, 5537–5540.
11. Cabiddu, S.; Fattuoni, C.; Floris, C.; Gelli, G.; Melis, S. *J. Organomet. Chem.* **1991**, *419*, 1–8.
12. Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515–1516.
13. Angeloni, A. S.; Pappalardo, G. *Gazz. Chim. Ital.* **1961**, *91*, 633–640.