N-Monomethylation of Primary Amines *via* Intermediate Benzothiazol-2(3*H*)-imines

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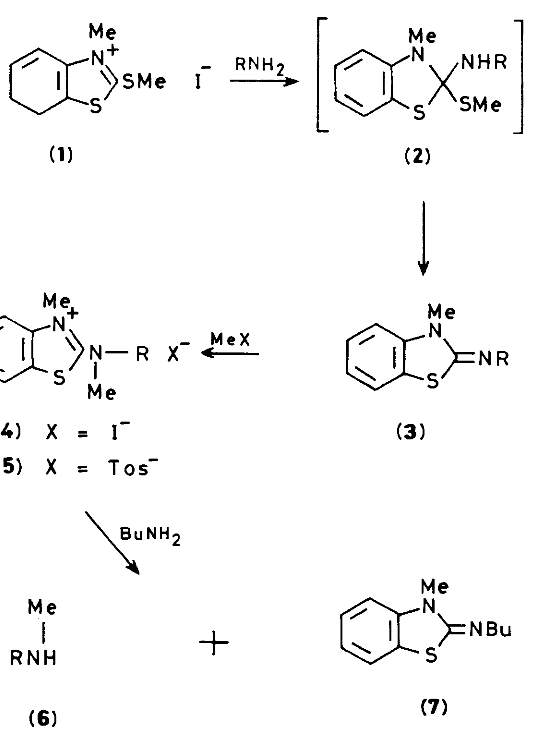
Aliphatic and aromatic amines are converted by successive treatment with (i) 3-methyl-2-methylthiobenzothiazolium iodide, (ii) methyl iodide or toluene-*p*-sulphonate, and (iii) butylamine, in high yield under mild conditions into their mono-*N*-methyl derivatives.

Although many methods are available for the *N*-alkylation of primary amines utilizing electrophilic alkylating agents,[1] most suffer from limitations that include competing bisalkylation, poor yields, and drastic reaction conditions (high temperatures, sealed tubes, *etc.*). In particular, none of the published procedures offer simultaneously mild conditions and simple, readily available reagents. While conceptually different approaches to the problem are available, among them the reduction of *N*-acyl[2] or imine[3] derivatives, and the nucleophilic addition of organolithium[4] and Grignard[5] reagents to formaldehyde imine intermediates, we considered worthwhile the development of a method for the monomethylation of primary amines using conventional electrophilic alkylating agents under mild conditions.



Scheme.

The benzothiazole ring 2-position shows high reactivity toward nucleophiles.[6,7] We have already taken advantage of this in earlier work on 2-alkylthiobenzothiazoles which has resulted in the development of novel methods for mercaptomethylation[8a] and mercaptoalkylation;[8b] the 2-alkylthiobenzothiazoles acting as protected thiols. Likewise, 2-substituted-3-methyl-2,3-dihydrobenzothiazoles have been used as protected forms for the carbonyl functionality.[9]

We now report the monomethylation of primary amines *via* 3-methylbenzothiazol-2(3*H*)-imines in a three-step sequence (see the Scheme) that includes (*a*) nucleophilic attack on 3-methyl-2-methylthiobenzothiazolium iodide (**1**) by primary amines to form 3-methylbenzothiazol-2(3*H*)-imines (**3**), (*b*) *N*-methylation of (**3**) on the imino nitrogen to afford the corresponding 3-methyl-2-(substituted amino)benzothiazolium salts (**4**) or (**5**), and (*c*) nucleophilic attack on the aminothiazolium salts (**4**) or (**5**) to liberate the *N*-methylated amines (**6**).

This sequence ensures exclusive monomethylation, the three steps each proceed in very high yield (see the Table), and the method is suitable for both aliphatic and aromatic amines.

3-Methylbenzothiazol-2(3*H*)-imines (**3**) are formed readily at room temperature in dichloromethane upon addition to (**1**) of 2 moles of a primary aliphatic amine or of one mole each of an aromatic amine and of triethylamine. The use of triethylamine instead of a second mole of the aromatic amine is required to complete the reaction, as the aromatic amine is not basic enough to promote β-elimination in the intermediate (**2**).

The methylation of the benzothiazol-2(3*H*)-imines derived from aliphatic amines takes place smoothly in refluxing methyl iodide over a 45 h period. Under these conditions, the methylations of the imines derived from aromatic amines are too slow to be of preparative utility. However, these conversions are conveniently carried out by heating together the amidine and methyl toluene-*p*-sulphonate at 100 °C for 1 h. This second method is general since it also works satisfactorily with aliphatic amines (see the Table).

The liberation of the *N*-methylated amines (**6**) from the amidinium salts (**4**) or (**5**) is achieved simply by treatment with one equivalent of butylamine in dichloromethane at 25 °C. The by-product 2-butylimino-3-methylbenzothiazole (**7**) is easily separated (for details see the Experimental section) and no side-reactions are observed.

All products were characterized by their spectral (i.r., ^{1}H and ^{13}C n.m.r.) properties, as well as elemental (C, H, N) analyses or by comparison of the boiling points and ^{1}H n.m.r. data with reported values in the case of *N*-methylated amines.

All the imines (**3**) showed a strong absorption in the region 1 635—1 610 cm^{-1} of their i.r. spectra, due to the C=N stretching vibrations. For the 2-aminobenzothiazolium salts (**4**) and (**5**), a medium intensity absorption appears at lower frequency (*ca.* 1 600 cm^{-1}).

The ^{13}C n.m.r. spectra of the imines (**3**) displayed characteristic absorptions for the benzothiazole quaternary carbons and for C-4. Thus, C-2, C-3a, and C-7a appeared at δ 157.0—153.4, 141.2—140.5, and 122.5—122.1, respectively, whereas C-4 was significantly shielded[10] at δ 108.9—108.0. The ^{1}H n.m.r. spectra of the imines (**3**) showed aromatic absorptions between δ 7.5 and 6.7, with 4-H being furthest upfield at about δ 6.8.

A large downfield shift in the ^{13}C n.m.r. spectra of the 2-aminobenzothiazolium salts (**4**) and (**5**) was observed for the benzothiazole C-2 (δ 170) with respect to the same carbon in (**3**),

Table. Preparation of amidines (3), amidinium salts (4) and (5), and *N*-methyl amines (6)

Starting amine	Amidine (3) (Method)	Yield of (3) (%)	Salts (4), (5)	Anion	Yield of (4), (5) (%)	NMe Amine	Yield[a] of (6) (%)	B.p. (°C/mmHg)[b]	Lit. b.p. °C/mmHg
Octylamine	(**3a**) (A)	95	(**4a**)	I^-	88	(**6a**)	88[d]	125—135/90	77.5—80/17[12]
Dodecylamine	(**3b**) (A)	95	(**4b**)	I^-	92	(**6b**)	85[c]	110—120/1.5	175—176[13]
Phenethylamine	(**3c**) (A)	98	(**4c**)	Tos^-	94	(**6c**)	85[d]	110—115/35—40	112—115/36—40[14a]
Cyclohexylamine	(**3d**) (A)	92	(**4d**)	I^-	98[e]	(**6d**)	83[d]	110—120/200	61—63/35[14b]
Aniline	(**3e**) (B)	98	(**5e**)	Tos^-	96	(**6e**)	88[f]	80—90/15	79.2/10[14c]
p-Toluidine	(**3f**) (B)	98	(**5f**)	Tos^-	98	(**6f**)	84[f]	92—95/8	98—99/19[14d]

[a] All yields based on isolated pure products as deducted from t.l.c. and ^1H n.m.r. spectroscopy. [b] Kugelrohr distillation; oven temperature. [c] Ether (10 ml) was added to the residue after evaporation of CH_2Cl_2, the precipitated amine hydroiodide was removed by filtration, treated with KOH and ethanol according to the general procedure that was followed thereafter. [d] Separated from (**6**) by direct distillation from the reaction mixture. [e] Based on recovered starting material. The conversion was 61%. [f] Separated from (**7**) by column chromatography (CH_2Cl_2).

whereas C-3a and C-7a remained at about the same chemical shifts. The C-4 signal was also shifted downfield to δ 114.1—113.8. A similar effect was observed in the ^1H n.m.r. spectra of the salts (**4a**) and (**5**) where 4-H resonated at δ 7.9—7.7.

Conclusion

The use of *N*-methylbenzothiazol-2(3*H*)-imines derived from primary amines allows exclusive monomethylation at the imino nitrogen. The *N*-methylated amines are easily liberated from this masked form and isolated in high overall yield. The sequence is general for both aliphatic and aromatic amines, and, with the exception of the methylation of amidines derived from aromatic amines, all the steps can be performed at or near room temperature. Therefore, the new method allows the monomethylation of primary amines under mild conditions with readily available reagents.

Experimental

Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 283B spectrophotometer and only selected absorptions are given. ^1H N.m.r. spectra were obtained on a Varian EM 360L (60 MHz; continuous wave mode) spectrometer, if unspecified, or Varian XL200 (200 MHz; FT mode) spectrometer, as specified, with Me_4Si as the internal standard. ^{13}C N.m.r. spectra were run on a Varian XL200 (50 MHz) spectrometer. Column chromatography was carried out using MCB silica gel (230—400 mesh).

3-Methyl-2-methylthiobenzothiazolium iodide (**1**) was prepared according to the literature procedure,[11] m.p. 145—147 °C (decomp.) [lit.,[11] m.p. 148 °C (decomp.)].

General Procedure for the Preparation of N-*Methylbenzothiazol*-2-(3H)-*imines* (3).—*Method A.* To a stirred suspension of (**1**) (2.9 g, 9 mmol) in methylene dichloride (45 ml) was added the aliphatic primary amine (18 mmol) and the suspension was stirred at 25 °C for the appropriate time (see below). The whole suspension was then extracted with water (3 × 50 ml), the organic layer was dried ($MgSO_4$), and the solvent evaporated to afford the amidines (**3**), that were pure (by t.l.c. and ^1H n.m.r. spectroscopy) in most cases.

Method B. The aromatic primary amine (9 mmol) and triethylamine (9 mmol) were added.

3-*Methyl*-2-*octylimino*-2,3-*dihydrobenzothiazole* (**3a**). Prepared (95%) from octylamine after 3 h of stirring, as an oil, b.p. (Kugelrohr) 130—137 °C/0.5 mmHg (Found: C, 69.5; H, 8.7; N, 10.1. $C_{16}H_{24}N_2S$ requires C, 69.6; H, 8.7; N, 10.1%); $\nu_{max.}$(neat) 1 630s and 1 585s cm^{-1}; $\delta_H(CDCl_3)$ 7.6—6.9 (4 H, m), 3.5 (3 H, s), 3.3 (2 H, t, *J* 7 Hz), and 1.9—0.8 (15 H, m); δ_C(50 MHz; $CDCl_3$) 155.5, 141.1, 126.1, 122.5, 121.9, 120.5, 108.3, 54.9, 31.7, 30.8, 29.7, 29.6, 29.3, 29.1, 22.5, and 13.9.

2-*Dodecylimino*-3-*methyl*-2,3-*dihydrobenzothiazole* (**3b**). Prepared (95%) from dodecylamine after 4 h of stirring, as an oil, b.p. (Kugelrohr) 140—150 °C/2 mmHg; $\nu_{max.}(CHBr_3)$ 1 630s and 1 585s cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.31—6.79 (4 H, m), 3.43 (3 H, s), 3.19 (2 H, t, *J* 7 Hz), 1.72—1.65 (2 H, m), 1.44—1.27 (18 H, m), and 0.92—0.86 (3 H, m); δ_C(50 MHz; $CDCl_3$) 155.4, 141.3, 126.0, 122.5, 121.9, 120.4, 108.2, 55.15, 31.9, 31.0, 29.8, 29.6, 29.5, 29.3, 27.5, 22.7, and 14.1 (Found: M^+, 332.2274. Calc. for $C_{20}H_{32}N_2S$: *M*, 332.2286).

3-*Methyl*-2-*phenethylimino*-2,3-*dihydrobenzothiazole* (**3c**). Prepared (98%) from phenethylamine, reaction time 3 h, yellowish oil, b.p. (Kugelrohr) 150—160 °C/2.5—3 mmHg (Found: C, 71.4; H, 6.1; N, 10.4. $C_{16}H_{16}N_2S$ requires C, 71.6; H, 6.0; N, 10.4%); $\nu_{max.}$(neat) 1 625s and 1 580s; $\delta_H(CDCl_3)$ 7.2—6.25 (9 H, m) and 3.5—2.5 (7 H, m); δ_C(50 MHz; $CDCl_3$) 155.7, 140.9, 128.7, 128.2, 125.9, 125.8, 121.8, 120.3, 108.1, 56.4, 37.3, and 29.8.

2-*Cyclohexylimino*-3-*methyl*-2,3-*dihydrobenzothiazole* (**3d**). Prepared from cyclohexylamine, reaction time 8 h. The oil was purified by column chromatography (chloroform) to afford pure (**3d**) (85%), b.p. (Kugelrohr) 115—120 °C/2 mmHg (Found: C, 68.2; H, 7.3; N, 11.3. $C_{14}H_{18}N_2S$ requires C, 68.2; H, 7.3; N, 11.4%); $\nu_{max.}$(neat) 1 610s and 1 580s cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.27—6.75 (4 H, m), 3.35 (3 H, s), 2.98—2.78 (1 H, m), 1.81 (5 H, m), and 1.39—1.37 (5 H, m); δ_C(50 MHz; $CDCl_3$) 153.4, 141.2, 125.9, 122.5, 121.8, 120.3, 108.0, 64.4, 33.8, 30.1, 25.7, and 25.0.

3-*Methyl*-2-*phenylimino*-2,3-*dihydrobenzothiazole* (**3e**). Prepared (98%) from aniline, reaction time 8 h, white microcrystals, m.p. 96—98 °C (from ethanol) (Found: C, 70.0; H, 5.1; N, 11.5. $C_{14}H_{12}N_2S$ requires C, 70.0; H, 5.0; N, 11.6%); $\nu_{max.}(CHBr_3)$ 1.620s and 1.580s cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.38—6.87 (9 H, m) and 3.53 (3 H, s); δ_C (50 MHz; $CDCl_3$) 157.0, 151.1, 140.5, 129.4, 126.1, 123.5, 122.2, 121.5, 121.4, 108.8, and 30.3.

3-*Methyl*-2-(p-*tolylimino*)-2,3-*dihydrobenzothiazole* (**3f**). Prepared from *p*-toluidine, reaction time 8 h. The residue from evaporation was triturated in ethanol to afford pure (**3f**) (94%), m.p. 89—91 °C (Found: C, 70.6; H, 5.5; N, 11.0. $C_{15}H_{14}N_2S$ requires C, 70.8; H, 5.55; N, 11.0%); $\nu_{max.}(CHBr_3)$ 1 620m and 1 580m cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.23—6.84 (8 H, m), 3.50 (3 H, s), and 2.32 (3 H, s); δ_C(50 MHz; $CDCl_3$) 157.0, 148.8, 140.7, 133.0, 130.2, 126.2, 122.4, 122.1, 121.6, 121.3, 108.9, 30.5, and 21.1.

General Procedure for the Methylation of the Imines (3).—(*a*) *Iodide salts* (4). The imine (**3**) (4.18 mmol) was refluxed in methyl iodide (20 ml) for 45 h. The solvent was distilled off and the solid remaining was triturated with ether, filtered, and washed with ether to afford the pure (based on t.l.c. and ^{1}H n.m.r. spectroscopy) iodides (**4**).

(*b*) *Toluene*-p-*sulphonate salts* (**5**). The imine (**3**) (1 mmol) was mixed with methyl toluene-*p*-sulphonate (1.6 mmol) and the mixture was heated at 100 °C for 1 h. The gummy material obtained was triturated with ether and the resulting white solid was filtered off and washed with ether. This gave the pure (based on t.l.c. and ^{1}H n.m.r. spectroscopy) salts (**5**).

3-*Methyl*-2-(N-*methyloctylamino*)*benzothiazolium iodide* (**4a**). Prepared (94%) from (**3a**), m.p. 107—114 °C (Found: C, 48.8; H, 6.6; N, 6.6. $C_{17}H_{27}IN_2S$ requires C, 48.8; H, 6.45; N, 6.7%); $\nu_{max.}$($CHBr_3$) 1605m and 1 570m cm^{-1}; δ_H($CDCl_3$) 8.3—7.5 (4 H, m), 4.3 (3 H, s), 3.9 (2 H, t, *J* 6 Hz), 3.75 (3 H, s), 1.9—1.8 (2 H, m), and 1.7—0.8 (13 H, m); δ_C 170.6, 140.4, 128.4, 125.8, 122.6, 121.4, 114.1, 58.8, 43.3, 39.3, 31.2, 28.65, 28.6, 26.3, 26.1, 22.1, and 13.6.

3-*Methyl*-2-(N-*methyldodecylamino*)*benzothiazolium iodide* (**4b**). Prepared (92%) from (**3b**), m.p. 123—125 °C (Found: C, 53.0; H, 7.6; N, 5.8. $C_{21}H_{35}IN_2S$ requires C, 53.1; H, 7.4; N, 5.9%); $\nu_{max.}$($CHBr_3$) 1 605s and 1 580s cm^{-1}; δ_H($CDCl_3$) 8.2—7.3 (4 H, m), 4.3 (3 H, s), 4.0—3.6 (5 H, m), 2.0—1.1 (20 H, m), and 0.9—0.8 (3 H, m); δ_C(50 MHz; $CDCl_3$) 170.6, 140.4, 128.4, 125.8, 122.5, 121.45, 114.1, 58.9, 43.3, 39.4, 29.1, 29.0, 28.9, 28.7, 26.3, 26.1, 22.2, and 13.7.

3-*Methyl*-2-(N-*methylphenethylamino*)*benzothiazolium toluene*-p-*sulphonate* (**5c**). Prepared (94%) from (**3c**), m.p. 145—147 °C (Found: C, 63.0; H, 6.0; N, 6.1. $C_{24}H_{26}N_2O_3S_2$ requires C, 63.4; H, 5.8; N, 6.2%); $\nu_{max.}$($CHBr_3$) 1 580m cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.66—6.93 (13 H, m), 3.90—3.70 (5 H, m), 3.45 (3 H, s), 2.99 (2 H, m), and 2.20 (3 H, s); δ_C(25 MHz; $CDCl_3$) 170.6, 143.5, 140.2, 138.6, 136.4, 128.4, 128.0, 126.7, 125.4, 121.9, 113.8, 59.3, 42.5, 37.5, 32.4, and 20.8.

3-*Methyl*-2-(N-*methylcyclohexylamino*)*benzothiazolium iodide* (**4d**). Prepared (99%) from (**3d**), m.p. 176—178 °C (Found: C, 46.15; H, 5.5; N, 7.0. $C_{15}H_{21}IN_2S$ requires C, 46.4; H, 5.45; N, 7.2%); $\nu_{max.}$($CHBr_3$) 1 590m and 1 560s cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.92 (1 H, d, *J* 8 Hz), 7.65—7.50 (2 H, m), 7.43 (1 H, d, *J* 8 Hz), 4.18 (3 H, s), 3.90—3.80 (1 H, m), 3.51 (3 H, s), and 2.30—1.50 (10 H, m); δ_C(25 MHz; $CDCl_3$) 170.7, 140.2, 128.2, 125.6, 122.4, 114.1, 66.7, 39.9, 37.5, 28.3, 24.6, and 24.3.

3-*Methyl*-2-(N-*methylanilino*)*benzothiazolium toluene*-p-*sulphonate* (**5e**). Prepared (96%) from (**3e**), m.p. 152—154 °C (Found: C, 62.3; H, 5.3; N, 6.4. $C_{22}H_{22}N_2O_3S_2$ requires C, 61.9; H, 5.2; N, 6.6%); $\nu_{max.}$($CHBr_3$) 1 595m and 1 565m cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8 Hz), 7.58—7.36 (9 H, m), 6.88 (2 H, d, *J* 6 Hz), 3.78 (3 H, s), 3.42 (3 H, s), and 2.19 (3 H, s); δ_C(25 MHz; $CDCl_3$) 169.6, 143.9, 143.0, 140.1, 138.1, 130.2, 129.0, 128.2, 127.8, 125.6, 125.4, 125.3, 123.9, 122.3, 113.9, 46.9, 36.8, and 20.8.

3-*Methyl*-2-(N-*methyl*-p-*toluidino*)*benzothiazolium toluene*-p-*sulphonate* (**5f**). Prepared (95%) from (**3f**), m.p. 186—188 °C (Found: C, 63.1; H, 5.7; N, 6.2. $C_{23}H_{24}N_2O_3S_2$ requires C, 62.7; H, 5.5; N, 6.4%); $\nu_{max.}$($CHBr_3$) 1 600m and 1 565s cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.75—7.23 (10 H, m), 6.91 (2 H, d, *J* 7 Hz), 3.77 (3 H, s), 3.45 (3 H, s), 2.37 (3 H, s), and 2.21 (3 H, s); δ_C (50 MHz; $CDCl_3$) 170.0, 144.2, 140.9, 140.6, 139.7, 138.3, 131.1, 128.4, 128.1, 125.9, 125.7, 125.6, 123.9, 122.6, 114.1, 47.4, 37.1, and 21.1.

General Procedure for the Preparation of N-*Methylated Amines* (**6**). The amidinium salt (**4**) or (**5**) (2 mmol) was dissolved in CH_2Cl_2 [4 ml for iodides (**4**) or 8 ml for toluene-p-*sulphonates* (**5**)], butylamine (2 mmol) was added with stirring and the solution was stirred at 25 °C for 3 h. The solvent was removed under reduced pressure (25 °C/35 mmHg) and the residue was dissolved in 95% ethanol (1 ml). Potassium hydroxide (1 g) was added to the solution, upon which a precipitate appeared, and the mixture was stirred at 25 °C for 3 h. Water (4 ml) was added and the solution was extracted with diethyl ether (4 × 10 ml). The ether extracts were washed with water (5 ml), dried ($MgSO_4$), and the solvent was evaporated (25 °C/35 mmHg) to give an oil that consisted of a mixture of the butyl imine (**7**) and the amine (**6**). The amine (**6**) was separated from (**7**) and purified as indicated in the Table. The boiling points (Table) and ^{1}H n.m.r. data of the amines (**6**) were in agreement with values reported in the literature. Data for compound (**7**) (average yield, 95%): oil, b.p. 99—104 °C/1.5 mmHg (Found: C, 65.5; H, 7.3; N, 12.7. $C_{12}H_{16}N_2S$ requires C, 65.4; H, 7.3; N, 12.7%); $\nu_{max.}$(neat) 1 635s and 1 590s cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.27 (1 H, d, *J* 7 Hz), 7.11 (1 H, t, *J* 8 Hz), 6.89 (1 H, t, *J* 8 Hz), 6.75 (1 H, d, *J* 8 Hz), 3.33 (3 H, s), 3.17 (2 H, t, *J* 7 Hz), 1.67 (2 H, quintet, *J* 7 Hz), 1.43 (2 H, sextet, *J* 7 Hz), and 0.95 (3 H, t, *J* 7 Hz); δ_C(50 MHz; $CDCl_3$) 155.2, 141.0, 125.9, 122.3, 121.7, 120.2, 107.9, 54.6, 39.2, 29.8, 20.4, and 13.9.

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