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Synthetic Elaboration of *N*-Substituents in Thioamides

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Abstract: *N*-(Benzotriazol-1-ylmethyl)arylthioamides, readily prepared from arylthioamides, formaldehyde and benzotriazole, undergo lithiation followed by reactions with alkyl halides, aldehydes and ketones to introduce the expected *N*-substituents into the *N*-methylene group. Subsequent displacements of the benzotriazolyl group by Grignard reagents, alkoxide or thioalkoxide anions provide general access to a wide variety of *N*-substituted thioamides in good yields.

N-Alkylation of amides[1] is generally accomplished by treatment with alkyl halides under a variety of basic conditions (KOH, NaH, LiH, Na, etc.),[2-8] although the amide anions sometimes undergo simultaneous *O*-alkylation. The direct *N*-alkylation of thioamides is, by contrast, rare owing to the strong nucleophilicity of the S-atom of the thiocarbonyl group. Alkylating agents, such as alkyl halides or tosylates, react at the S-atom of thioamides to yield *S*-alkylthioimidolium salts which, on deprotonation, form thioimidates.[9-11] Only a limited number of alkylating agents, those which can form stable carbocations, such as triphenylmethyl chloride,[12] benzhydrol,[13] and xanthydryl alcohol,[13] have successfully *N*-alkylated thioamides. Such *N*-alkylation has been interpreted in terms of thermodynamically stable *N*-alkylation where the kinetically favored *S*-alkylation is reversible.[10,12,13] Indeed, such *N*-alkylations occur only under conditions that favor formation of stabilized carbonium ions. The generally greater stability of the *N*-alkylated products is confirmed by the rearrangement of *S*-arylalkylimidothiolates on treatment with dilute acid or by heating into the *N*-substituted thioamides.[13]

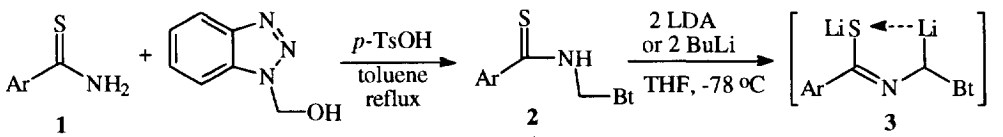
Reactions of thioamides and aldehydes yield the corresponding *N*-(hydroxyalkyl)thioamides, which then react with amines to form Mannich bases.[14-17] Such *N*-(hydroxymethyl)thioamides derived from formaldehyde have also been converted into *N*-alkoxymethyl[18] or *N*-chloromethyl[18] derivatives by treatment with alcohols or thionyl chloride, respectively. Giordano *et al*[19] reported the preparation of *N*-(α-alkoxyalkyl)thioamides from thioamides and acetals. Lithiation in *N*-methyl groups of thioamides was reported[20] for *N,N*-dimethylthiopivalamide and for lithium *N*-methyldithiocarbamates[21] together with subsequent reactions with electrophiles.

We have demonstrated that the benzotriazole anion is a good activating and leaving group and can be used in place of a halogen or other substituents in many transformations.[22-23] In particular, benzotriazole-

mediated synthetic methodology has opened a new route for the preparative introduction of a diverse range of *N*-substituents into secondary and tertiary amides.[24-29] We have previously demonstrated that thioamides can also be readily *N*-alkylated in a two-step procedure: (i) reaction with an aldehyde and benzotriazole to yield an adduct, (ii) displacement of the benzotriazolyl group by hydride ($NaBH_4$), or by alkyl anions (Grignard reagents).[30-31] In these reactions with thioamides, the benzotriazole-stabilized cation $BtCH_2^+$, formed by dehydration of 1-hydroxymethylbenzotriazole in an acidic medium, leads to exclusive *N*-alkylation rather than the *S*-alkylation observed with conventional alkylating agents. This approach provided a convenient and general access to the *N*-alkylation of thioamides. Recently, *N*-(benzotriazol-1-ylmethyl)benzamide and *N*-(benzotriazol-1-ylmethyl)trimethylacetamide were shown to undergo facile lithiation at the methylene group, and subsequent quenching with various electrophiles gave the corresponding *N*-substituted derivatives.[32] This provides an alternative for the preparation of more complex and functionalized *N*-substituted amides especially in those cases where the aldehydes required for direct condensation are unstable or are not readily available. An analogous approach involving lithiation is now described for the elaboration of arylthioamides in which a range of nucleophiles (Grignard reagents, RO^-, and RS^-) have been employed for the displacement of benzotriazole to give a variety of *N*-substituted arylthioamides.

RESULTS AND DISCUSSION

According to the previously described procedure,[30-31] *N*-(benzotriazol-1-ylmethyl)thioamides **2a,b** were readily prepared in 71-72% yields by refluxing the corresponding thioamides **1a,b** and 1-hydroxymethylbenzotriazole in toluene with *p*-toluenesulfonic acid catalysis. Treatment of **2a** with two equiv of butyllithium or LDA at -78 °C under nitrogen formed dianion **3a** (see Scheme 1). This intermediate was trapped with ethyl bromide to give **4a** in 95% yield. Compounds **4b-j** were similarly obtained from *N*-(benzotriazol-1-ylmethyl)thioamides **2a,b** and the corresponding electrophiles in 40-95% yields. The reactions need to be quenched at -78 °C to avoid the decomposition which occurs at higher temperatures due to the presence of another molecule of lithium salt. It is noteworthy that compound **4e**, obtained *via* lithiation followed by trapping with allyl bromide, is not easily accessible by our previous method employing direct



1,2,3 a Ar = Ph
b Ar = 4-ClC_6H_4

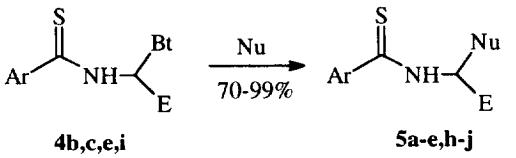
Bt =

4	Ar	E
a	Ph	Et
b	Ph	*n*-Bu
c	Ph	*n*-C_7H_{15}
d	Ph	*n*-C_8H_{17}
e	Ph	allyl
f	Ph	PhCH(OH)
g	Ph	$C_6H_{13}CH(OH)$
h	Ph	$(CH_3)_2C(OH)$
i	4-ClC_6H_4	*n*-Bu
j	4-ClC_6H_4	allyl

Scheme 1

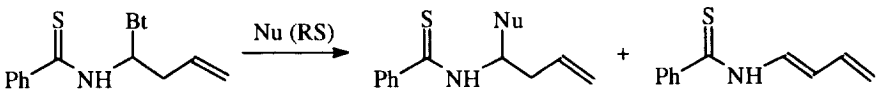
condensation of a thioamide, aldehyde and benzotriazole due to the expected isomerization of the β,γ-unsaturated aldehyde during the reaction. Furthermore, the present method allows easy introduction of a β-hydroxy group into the *N*-substituents when the dianions **3** are reacted with a ketone or an aldehyde (**4f-h**).

Displacements of the benzotriazole group in thioamide derivatives of type **4a-d** by Grignard reagents and hydrides($NaBH_4$) have been previously reported.[30-31] We now find that the introduction of an allyl group to the α-position relative to the benzotriazolyl group allows the reaction with Grignard reagents to be performed under milder conditions. Thus, treatment of compound **4e** with *n*-butylmagnesium bromide in THF at 30 °C for 10 h gave the expected product **5a** in 70% yield (Scheme 2). Amide **5b** was similarly prepared in 83% yield.



4b,c,e,i **5a-e,h-j**

5	Ar	E	Nu
a	Ph	allyl	*n*-Bu
b	Ph	allyl	Ph
c	Ph	allyl	OMe
d	Ph	allyl	OEt
e	Ph	*n*-Bu	OMe
f	Ph	allyl	SBu
g	Ph	allyl	SPr*i*
h	Ph	*n*-C_7H_{15}	SPr*i*
i	4-ClC_6H_4	allyl	OEt
j	4-ClC_6H_4	*n*-Bu	SPr*i*



4e **5f,g** (41-45%) **6** (19-20%)

Scheme 2

Displacement of the benzotriazole moiety by other nucleophiles, such as RO^-, RS^-, etc., provides a convenient route for the synthesis of various *N*-alkoxyalkyl and *N*-thioalkoxyalkyl substituted thioamides. We have now carried out a number of such transformations to demonstrate the generality of the present method (see Scheme 2). Thus, heating a mixture of *N*-[α-(benzotriazol-1-yl)buten-3-yl]thiobenzamide **4e** and NaOMe in MeOH at 50 °C for 14 h gave the product **5c** in 75% yield. Compounds **5d**, **5e**, and **5i** were similarly prepared in 74-99% yields. When *N*-[α-(benzotriazol-1-yl)buten-3-yl]thiobenzamide **4e** was treated with sodium thiobutoxide or *iso*-thiopropoxide at room temperature for 16 h, the expected *N*-(α-alkylthioalkyl)thioamides **5f,g** were obtained in 41-45% yields, respectively. The elimination product **6**, *N*-(1,3-butadienyl)thiobenzamide, was simultaneously afforded (19-20%) because basic thioalkoxides extrude a β-hydrogen and the subsequent removal of benzotriazole yields the conjugated product. However, similar treatment of compounds **4c** and **4i** gave only the expected amides **5h** and **5j** in 98% and 70% yields, respectively, and no elimination products were detected.

The structures of all intermediates **4** and the final products **5** and **6** were confirmed by their ^1H NMR, and ^{13}C NMR spectra and elemental analysis or HRMS. The ^{13}C signals of the methine group in intermediates **4a-j** were shifted downfield (66.7-72.2 ppm) compared to the signals of the methylene group (55.0-56.8 ppm) in **2a,b**. The NMR data clearly indicated the disappearance of the characteristic benzotriazolyl signals for amides **5a-j**. The data for known compounds are in agreement with those reported in the literature.

In conclusion, the present method provides a convenient route for the preparation of thioamides with complex *N*-substituents. Our method is versatile in the sense that (α-hydroxyalkyl) and γ,δ-unsaturated groups can be easily introduced to give compounds which are not accessible by previous methods.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini VXR 300 MHz spectrometer using TMS as the internal reference for ^{1}H spectra and $CDCl_3$ for ^{13}C spectra (unless otherwise stated). Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass measurements were performed on an AEI MS-30 mass spectrometer. Column chromatography was carried out on silica gel (230-400 mesh).

Compound **2a** was prepared according to the previously described method.[30-31] Compound **2b** was prepared by adaptation of the literature procedure.[30-31]

*N-(Benzotriazol-1-ylmethyl)-4-chlorothiobenzamide (**2b**).*

A mixture of 1-hydroxymethylbenzotriazole (2.98 g, 20 mmol), 4-chlorothiobenzamide **1b** (20 mmol) and a catalytic amount of *p*-toluenesulfonic acid (0.1 g, 0.5 mmol) was refluxed in toluene (100 ml) with a Dean-Stark trap for 24 hours. The solvent was removed under reduced pressure, and the crude product purified by recrystallization from benzene-ethanol (4:1): yield 72%; mp 244-245 °C (Found: C, 55.61; H, 3.61; N, 18.60. $C_{14}H_{11}N_4SCl$ requires C, 55.53; H, 3.66; N, 18.50); ^{1}H NMR (DMSO-d_6) δ 6.78 (d, 2 H, J = 6.1 Hz), 7.36 (d, 1 H, J = 8.5 Hz), 7.37-7.42 (m, 1 H), 7.52-7.58 (m, 1 H), 7.74 (d, 2 H, J = 8.4 Hz), 8.01 (t, 2 H, J = 7.4 Hz), 8.65-8.68 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 56.8, 111.2, 119.2, 124.3, 127.7, 128.2, 129.3, 132.6, 136.4, 138.8, 145.1, 199.1.

*General Procedure for the Preparation of N-(Benzotriazol-1-ylmethyl)thioamides **4a-j**.*

A solution of **2a,b** (2 mmol) in dry THF (80 ml) was cooled to -78 °C under nitrogen in a dry ice-acetone bath and a solution of *n*-butyllithium or lithium diisopropylamide (2.0 M, 2 ml, 4 mmol) was added slowly. The obtained dark-violet solution was stirred at this temperature for 20 min and then a solution of the corresponding electrophile (2 mmol) in dry THF (10 ml) was added dropwise. The resulting solution was stirred at -78 °C for 30 min, poured into 100 ml of ice-water and extracted with ether (for **4a-e,i,j**) or with ether-THF (for **4f-h**). The ethereal solution obtained was dried over $MgSO_4$. Removal of the solvents under reduced pressure yielded the crude product which was purified by recrystallization from ethanol or benzene (**4a-d** and **4j**), or by column chromatography (ethyl acetate/hexane = 1:4) (**4e-i**).

*N-[α-(Benzotriazol-1-yl)propyl]thiobenzamide (**4a**)*: yield 95%; mp 142-143 °C (Found: C, 65.14; H, 5.42; N, 18.85. $C_{16}H_{16}N_4S$ requires C, 64.84; H, 5.45; N, 18.92); ^{1}H NMR δ 0.99 (t, 3 H, J = 7.4 Hz), 2.54-2.64 (m, 2 H), 7.26-7.40 (m, 4 H), 7.48-7.55 (m, 2 H), 7.77 (d, 2 H, J = 7.3 Hz), 7.89 (d, 1 H, J = 8.3 Hz), 7.94 (d, 1 H, J = 8.3 Hz), 9.35 (d, 1 H, J = 8.5 Hz); ^{13}C NMR δ 9.7, 27.8, 68.8, 110.5, 119.5, 124.4, 127.1, 127.9, 128.4, 131.7, 133.3, 140.7, 145.2, 200.6.

*N-[α-(Benzotriazol-1-yl)pentyl]thiobenzamide (**4b**)*: yield 83%; mp 132-133 °C (Found: C, 66.89; H, 6.25; N, 17.18. $C_{18}H_{20}N_4S$ requires C, 66.63; H, 6.21; N, 17.27); ^{1}H NMR δ 0.88 (t, 3 H, J = 7.0 Hz), 1.20-1.50 (m, 4 H), 2.46-2.70 (m, 2 H), 7.30-7.64 (m, 6 H), 7.74 (d, 2 H, J = 7.0 Hz), 7.92 (d, 1 H, J = 8.4 Hz),

7.98 (d, 1 H, J = 8.4 Hz), 8.77 (d, 1 H, J = 8.4 Hz); ^{13}C NMR δ 13.8, 22.1, 27.1, 34.3, 67.3, 110.5, 119.7, 124.4, 127.0, 128.0, 128.5, 131.7, 133.3, 140.8, 145.4, 200.3.

*N-[α-(Benzotriazol-1-yl)octyl]thiobenzamide (**4c**):* yield 82%; mp 135-136 °C (Lit.[30-31] mp 134-136 ° C); ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 3 H, J = 6.8 Hz), 1.18-1.42 (m, 10 H), 2.51-2.64 (m, 2 H), 7.33-7.62 (m, 6 H), 7.71-7.75 (m, 2 H), 7.91 (d, 1 H, J = 8.4 Hz), 8.03 (d, 1 H, J = 8.4 Hz), 8.54 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9, 21.9, 24.6, 28.2, 28.3, 31.0, 33.0, 68.6, 111.0, 119.2, 124.1, 127.5, 128.0, 131.2, 132.2, 140.7, 144.9, 200.5.

*N-[α-(Benzotriazol-1-yl)nonyl]thiobenzamide (**4d**)*: yield 95%; mp 130-131 °C (Found: C, 69.47; H, 7.45; N, 14.72. $C_{22}H_{28}N_4S$ requires C, 69.44; H, 7.42; N, 14.73); ^{1}H NMR δ 0.82 (t, 3 H, J = 6.8 Hz), 1.15-1.45 (m, 12 H), 2.45-2.60 (m, 2 H), 7.25-7.65 (m, 6 H), 7.75 (d, 2 H, J = 7.2 Hz), 7.84 (d, 1 H, J = 8.3 Hz), 7.90 (d, 1 H, J = 8.3 Hz), 9.29 (d, 1 H, J = 8.8 Hz); ^{13}C NMR δ 13.9, 22.5, 25.0, 28.9, 29.0, 29.1, 31.6, 34.2, 67.5, 110.6, 119.4, 124.4, 127.1, 127.8, 128.3, 131.6, 133.2, 140.7, 145.2, 200.4.

*N-[α-(Benzotriazol-1-yl)buten-3-yl]thiobenzamide (**4e**)*: yield 83%; mp 145-146 °C (Found: C, 66.51; H, 5.35; N, 17.90. $C_{17}H_{16}N_4S$ requires C, 66.21; H, 5.23; N, 18.17); ^{1}H NMR δ 3.32 (t, 2 H, J = 7.0 Hz), 5.17 (d, 1 H, J = 10.2 Hz), 5.28 (d, 1 H, J = 17.0 Hz), 5.73-5.86 (m, 1 H), 7.30-7.70 (m, 6 H), 7.76 (d, 2 H, J = 7.8 Hz), 7.90 (d, 2 H, J = 8.8 Hz), 9.08 (d, 1 H, J = 7.1 Hz); ^{13}C NMR δ 38.5, 66.7, 110.5, 119.5, 120.5, 124.4, 127.1, 127.9, 128.4, 130.7, 131.7, 133.1, 140.7, 145.2, 200.5.

*N-[1-(Benzotriazol-1-yl)-2-hydroxy-2-phenylethyl]thiobenzamide (**4f**).* Obtained as a mixture of two diastereomers (4:1 from NMR, represented as ma: major and mi: minor): yield 62%; mp 212-213 °C (Found: C, 67.27; H, 4.87; N, 14.85. $C_{21}H_{18}N_4SO$ requires C, 67.36; H, 4.84; N, 14.96); ^{1}H NMR (DMSO-d_6) δ 5.60-5.66 (m, 1 H), 6.00 (d, J = 5.0 Hz, ma) and 6.39 (d, J = 4.9 Hz, mi) (total 1 H), 7.03-7.09 (m, 1 H), 7.25-7.80 (m, 12 H), 8.06 (d, 1 H, J = 8.4 Hz), 8.15 (d, 1 H, J = 8.4 Hz), 11.42 (d, J = 8.0 Hz, ma) and 11.62 (d, J = 8.0 Hz, mi) (total 1 H); ^{13}C NMR (DMSO-d_6) δ 72.0, 72.8, 111.7, 119.0, 123.9, 126.5, 127.3, 127.4, 127.6, 127.9, 128.0, 128.1, 128.2, 131.2, 133.8, 140.8, 200.7.

*N-[1-(Benzotriazol-1-yl)-2-hydroxyoctyl]thiobenzamide (**4g**).* Obtained as an oil (1:1 mixture of two diastereomers from NMR): yield 53% (Found: HRMS M+1 = 383.1909. $C_{21}H_{26}N_4SO$ requires M+1 = 383.1906); ^{1}H NMR δ 0.79-0.90 (m, 3 H), 1.10-1.80 (m, 10 H), 3.83-3.98 (m) and 4.32-4.48 (m) (total 1 H), 4.50-4.68 (m, 1 H), 7.30-7.60 (m, 6 H), 7.75-8.10 (m, 4 H), 9.12 (d, J = 6.0 Hz) and 9.35 (d, J = 5.6 Hz) (total 1 H); ^{13}C NMR δ 13.9 (14.0), 22.3 (22.5), 25.3 (25.5), 28.8 (29.0), 31.4 (31.6), 32.8 (33.4), 69.1 (69.3), 73.0 (73.5), 110.9 (111.1), 119.5, 124.6 (124.7), 126.9 (127.0), 128.2 (128.3), 128.4 (128.5), 131.8 (131.9), 133.9, 140.5, 144.9 (145.0), 200.4 (201.2).

*N-[1-(Benzotriazol-1-yl)-2-hydroxy-2-methylpropyl]thiobenzamide (**4h**)*: yield 40%; mp 141-142 °C (Found: C, 62.86; H, 5.67; N, 16.91. $C_{17}H_{18}N_4SO$ requires C, 62.55; H, 5.56; N, 17.16); ^{1}H NMR δ 1.04 (s, 3 H), 1.56 (s, 3 H), 4.10 (s, 1 H), 7.34-7.50 (m, 5 H), 7.53-7.60 (m, 1 H), 7.79 (d, 2 H, J = 8.2 Hz), 8.00-8.08 (m, 2 H), 9.14-9.18 (m, 1 H); ^{13}C NMR δ 26.0, 26.4, 72.2, 73.8, 110.8, 119.8, 124.7, 126.9, 128.4, 128.5, 131.9, 134.0, 140.5, 144.7, 201.0.

*N-[1-(Benzotriazol-1-yl)pentyl]-4-chlorothiobenzamide (**4i**)*: yield 65%; mp 135-136 °C (Found: HRMS M+1 = 359.1087. $C_{18}H_{19}N_4SCl$ requires M+1 = 359.1097); ^{1}H NMR δ 0.87 (t, 3 H, J = 7.0 Hz), 1.20-1.40 (m, 4 H), 2.45-2.65 (m, 2 H), 7.31 (d, 2 H, J = 8.7 Hz), 7.39 (t, 1 H, J = 7.3 Hz), 7.50-7.60 (m, 2 H), 7.72 (d, 2 H, J = 8.7 Hz), 7.90 (d, 1 H, J = 8.4 Hz), 7.96 (d, 1 H, J = 8.4 Hz), 8.96 (d, 1 H, J = 8.7 Hz); ^{13}C

NMR δ 13.7, 22.1, 27.1, 34.0, 67.6, 110.6, 119.4, 124.6, 128.0, 128.4, 128.5, 133.2, 138.0, 138.8, 145.1, 198.9.

*N-[α-(Benzotriazol-1-yl)buten-3-yl]-4-chlorothiobenzamide (**4j**)*: yield 65%; mp 178-180 °C (Found: C, 59.81; H, 4.38; N, 16.21. $C_{17}H_{15}N_4SCl$ requires C, 59.55; H, 4.41; N, 16.34); ^1H NMR (DMSO-d_6) δ 3.30 (t, 2 H, J = 7.0 Hz), 5.15 (dd, 1 H, J = 10.2 and 1.4 Hz), 5.30 (dd, 1 H, J = 17.0 and 1.4 Hz), 5.72-5.84 (m, 1 H), 7.32-7.45 (m, 3 H), 7.52-7.61 (m, 2 H), 7.69 (d, 2 H, J = 8.6 Hz), 7.87 (d, 1 H, J = 8.4 Hz), 8.02 (d, 1 H, J = 8.4 Hz), 8.59 (d, 1 H, J = 9.0 Hz); ^{13}C NMR (DMSO-d_6) δ 37.4, 67.8, 111.1, 119.2, 119.4, 124.1, 127.5, 128.1, 129.3, 131.9, 132.4, 136.1, 139.1, 144.8, 198.9.

*General Procedure for the Preparation of N-Alkylthiobenzamides **5a,b**.*

A solution of **4e** (0.62 g, 2 mmol) in THF (10 ml) was added dropwise to freshly prepared *n*-butylmagnesium bromide or phenylmagnesium bromide (1 M in ether, 10 ml, 10 mmol) and the obtained reaction mixture was heated at 30 °C for 10 hours. The reaction mixture was then poured into a saturated solution of NH_4Cl (30 ml) and extracted with ether (3 × 50 ml). The combined extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a crude product which was purified by column chromatography (ethyl acetate/hexane = 1:4).

*N-(1-Allylpentyl)thiobenzamide (**5a**).* Obtained as an oil: yield 70% (Found: C, 73.07; H, 8.48; N, 5.63. $C_{15}H_{21}NS$ requires C, 72.82; H, 8.56; N, 5.66); ^1H NMR δ 0.91 (t, 3 H, J = 7.0 Hz), 1.30-1.45 (m, 4 H), 1.62-1.72 (m, 2 H), 2.38-2.58 (m, 2 H), 4.78-4.88 (m, 1 H), 5.13 (s, 1 H), 5.17 (d, 1 H, J = 7.3 Hz), 5.80-5.93 (m, 2 H), 7.33-7.53 (m, 4 H), 7.67-7.75 (m, 2 H); ^{13}C NMR δ 14.0, 22.6, 28.1, 32.9, 37.6, 55.0, 118.5, 126.5, 128.4, 130.8, 133.7, 142.5, 198.5.

*N-(1-Phenylbuten-3-yl)thiobenzamide (**5b**)*: yield 83%; mp 78-79 °C (Found: C, 76.39; H, 6.38; N, 5.19. $C_{17}H_{17}NS$ requires C, 76.36; H, 6.41; N, 5.24); ^1H NMR δ 2.73-2.92 (m, 2 H), 5.14-5.28 (m, 2 H), 5.73-5.92 (m, 2 H), 7.25-7.50 (m, 8 H), 7.70-7.76 (m, 2 H), 7.77-7.88 (m, 1 H); ^{13}C NMR δ 39.6, 58.4, 118.9, 126.6, 126.7, 128.5, 128.8, 131.1, 133.5, 140.0, 142.1, 198.5.

*General Procedure for the Preparation of N-(α-Alkoxyalkyl)arylthioamides **5c-e,i**.*

Compound **4b, 4e** or **4j** (2 mmol) was added in one portion to a solution of sodium alkoxide (6 mmol) in the corresponding alcohol (15 ml) at room temperature. The obtained solution was stirred at 50 °C for 14 hours until the starting material had been consumed (by TLC). The resulting reaction mixture was poured into 50 ml of ice water and extracted with ether (3 × 30 ml). The organic extracts were dried over $MgSO_4$, and the residue obtained after evaporation of the solvent was chromatographed (ethyl acetate/hexane = 1:4) to give the corresponding product.

*N-(1-Methoxybuten-3-yl)thiobenzamide (**5c**).* Obtained as an oil: yield 75% (Found: C, 65.02; H, 6.74; N, 6.25. $C_{12}H_{15}NSO$ requires C, 65.12; H, 6.83; N, 6.33); ^1H NMR δ 2.50-2.70 (m, 2 H), 3.50 (s, 3 H), 5.18 (s, 1 H), 5.22 (d, 1 H, J = 6.4 Hz), 5.83-6.02 (m, 2 H), 7.36-7.51 (m, 3 H), 7.63-7.68 (m, 1 H), 7.70-7.78 (m, 2 H); ^{13}C NMR δ 38.8, 57.0, 86.1, 119.3, 126.5, 128.5, 131.4, 131.7, 141.7, 200.2.

*N-(1-Ethoxybuten-3-yl)thiobenzamide (**5d**)*: yield 77%; mp 70-71 °C (Found: C, 66.08; H, 7.18; N, 5.93. $C_{13}H_{17}NSO$ requires C, 66.34; H, 7.28; N, 5.95); ^1H NMR δ 1.23 (t, 3 H, J = 7.0 Hz), 2.53-2.69 (m, 2 H), 3.64-3.84 (m, 2 H), 5.17-5.26 (m, 2 H), 5.85-5.99 (m, 1 H), 6.03-6.10 (m, 1 H), 7.36-7.50 (m, 3 H), 7.66-7.77 (m, 3 H); ^{13}C NMR δ 15.2, 39.0, 64.9, 84.7, 119.1, 126.5, 128.5, 131.3, 131.9, 141.7, 199.7.

*N-(1-Methoxypentyl)thiobenzamide (**5e**)*: yield 99%; mp 77-78 °C (Found: C, 65.88; H, 8.25; N, 5.68. $C_{13}H_{19}NSO$ requires C, 65.78; H, 8.07; N, 5.90); ^{1}H NMR δ 0.92 (t, 3 H, *J* = 7.0 Hz), 1.30-1.50 (m, 4 H), 1.75-1.82 (m, 2 H), 3.48 (s, 3 H), 5.91 (dt, 1 H, *J* = 6.0 and 7.8 Hz), 7.35-7.50 (m, 3 H), 7.64-7.72 (m, 1 H), 7.73-7.78 (m, 2 H); ^{13}C NMR δ 13.9, 22.4, 26.5, 34.5, 56.9, 87.4, 126.5, 128.4, 131.2, 141.7, 200.1.

*N-(1-Ethoxybuten-3-yl)-4-chlorothiobenzamide (**5i**)*: yield 74%; mp 83-85 °C (Found: C, 58.21; H, 5.80; N, 5.03. $C_{13}H_{16}NSOCl$ requires C, 57.87; H, 5.98; N, 5.19); ^{1}H NMR δ 1.23 (t, 3 H, *J* = 7.0 Hz), 2.50-2.70 (m, 2 H), 3.65-3.80 (m, 2 H), 5.15-5.25 (m, 2 H), 5.84-5.94 (m, 1 H), 5.98-6.08 (m, 1 H), 7.33-7.42 (m, 2 H), 7.60-7.77 (m, 3 H); ^{13}C NMR δ 15.9, 39.0, 65.1, 84.8, 119.3, 127.9, 128.1, 131.7, 137.7, 139.9, 198.1.

*General Procedure for the Preparation of N-(α-Alkylthioalkyl)thiobenzamides **5f-h,j** and Byproduct **6**.*

A mixture of the appropriate thiol (6 mmol) and sodium (0.14 g, 6 mmol) in 15 ml of dry THF was stirred at room temperature for 2 hours. A solution of **4c**, **4e** or **4i** (2 mmol) in THF (10 ml) was then added to the obtained suspension. The reaction mixture was stirred at room temperature for 16 hours, after which the resulting solution was poured into ice water (50 ml), extracted with ether (3 × 30 ml) and dried over $MgSO_4$. Evaporation of the solvent and the excess thiol under reduced pressure gave a residue which was purified by column chromatography (ethyl acetate/hexane = 1:4) to give the corresponding product. In the cases of **5f** and **5g**, *N*-(1,3-butadienyl)thiobenzamide **6** was obtained as a byproduct after column chromatography.

*N-(1-Butylthiobuten-3-yl)thiobenzamide (**5f**)*. Obtained as an oil: yield 45% (Found: C, 64.11; H, 7.46; N, 4.99. $C_{15}H_{21}S_2N$ requires C, 64.47; H, 7.58; N, 5.01); ^{1}H NMR δ 0.90 (t, 3 H, *J* = 7.1 Hz), 1.35-1.43 (m, 2 H), 1.55-1.70 (m, 2 H), 2.50-2.80 (m, 4 H), 5.14-5.24 (m, 2 H), 5.81-5.98 (m, 1 H), 6.08-6.16 (m, 1 H), 7.35-7.52 (m, 3 H), 7.65-7.82 (m, 3 H); ^{13}C NMR δ 13.6, 21.9, 30.9, 32.0, 39.2, 59.6, 119.2, 126.5, 128.5, 131.3, 132.5, 141.9, 198.3.

*N-(1-iso-Propylthiobuten-3-yl)thiobenzamide (**5g**)*. Obtained as an oil: yield 41% (Found: C, 63.01; H, 7.02; N, 5.24. $C_{14}H_{19}S_2N$ requires C, 63.35; H, 7.21; N, 5.28); ^{1}H NMR δ 1.27 (d, 3 H, *J* = 6.8 Hz), 1.40 (d, 3 H, *J* = 6.6 Hz), 2.66-2.71 (m, 2 H), 3.18 (hept, 1 H, *J* = 7.0 Hz), 5.17 (s, 1 H), 5.24 (d, 1 H, *J* = 7.3 Hz), 5.82-5.98 (m, 1 H), 6.08-6.16 (m, 1 H), 7.37-7.51 (m, 3 H), 7.60-7.74 (m, 3 H); ^{13}C NMR δ 23.4, 24.5, 35.4, 39.3, 58.9, 119.2, 126.5, 128.6, 131.3, 132.6, 141.2, 197.8.

*N-(1-iso-Propylthiooctyl)thiobenzamide (**5h**)*. Obtained as an oil: yield 98% (Found: C, 67.13; H, 9.35; N, 4.15. $C_{18}H_{29}S_2N$ requires C, 66.82; H, 9.03; N, 4.33); ^{1}H NMR δ 0.88 (t, 3 H, *J* = 7.0 Hz), 1.20-1.55 (m, 16 H), 1.76-1.94 (m, 2 H), 3.15 (hept, 1 H, *J* = 6.7 Hz), 6.00- 6.08 (m, 1 H), 7.37-7.53 (m, 3 H), 7.66 (d, 1 H, *J* = 8.7 Hz), 7.72-7.77 (m, 2 H); ^{13}C NMR δ 14.1, 22.6, 23.5, 24.6, 26.1, 29.1, 29.2, 31.7, 35.2, 59.9, 126.6, 128.5, 128.6, 131.2, 141.6, 197.5.

*N-(1-iso-Propylthiopentyl)-4-chlorothiobenzamide (**5j**)*. Obtained as an oil: yield 70% (Found: C, 56.99; H, 7.06; N, 4.36. $C_{15}H_{22}S_2NCl$ requires C, 57.02; H, 7.02; N, 4.43); ^{1}H NMR δ 0.92 (t, 3 H, *J* = 7.1 Hz), 1.26 (d, 3 H, *J* = 6.8 Hz), 1.39 (d, 3 H, *J* = 6.6 Hz), 1.35-1.50 (m, 4 H), 1.80-1.92 (m, 2 H), 3.10-3.18 (m, 1 H), 6.00 (dt, 1 H, *J* = 6.7 and 9.1 Hz), 7.37 (d, 2 H, *J* = 8.5 Hz), 7.60 (d, 1 H, *J* = 7.7 Hz), 7.68 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR δ 13.9, 22.3, 23.5, 24.6, 28.2, 35.0, 35.2, 60.1, 127.9, 128.7, 137.5, 139.8, 196.0.

*N-(1,3-Butadienyl)thiobenzamide (**6**)*: yield 19-20%; mp 105-108 °C (Found: C, 69.40; H, 6.05; N, 7.34. $C_{11}H_{11}NS$ requires C, 69.80; H, 5.86; N, 7.40); ^{1}H NMR δ 4.97 (dd, 1 H, *J* = 10.2 and 1.4 Hz), 5.11 (dd, 1 H, *J* = 17.0 and 1.5 Hz), 6.05 (dd, 1 H, *J* = 14.1 and 10.7 Hz), 6.30 (dt, 1 H, *J* = 17.0 and 10.5 Hz), 7.20 (dd,

1 H, J = 14.0 and 10.7 Hz), 7.38-7.54 (m, 3 H), 7.79-7.84 (m, 2 H), 8.32 (d, 1 H, J = 10.0 Hz); ^{13}C NMR δ 114.7, 126.2, 127.1, 127.2, 128.7, 132.0, 133.3, 134.5, 164.6.

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