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A GENERAL METHOD FOR THE N-ALKYLATION OF THIOAMIDES.[1]

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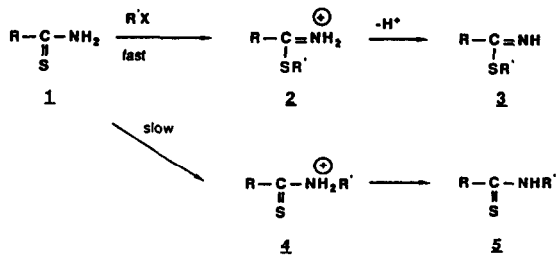
Abstract: Thioamides are N-alkylated in a two-step procedure: (i) Reaction with an aldehyde and benzotriazole yields an adduct which is (ii) reduced to the N-alkylthioamide by $NaBH_4$.

No generally applicable method has previously been available for the N-alkylation of thioamides. Alkyl halides, and other alkylating agents, as is well documented,[2,3] react at the S-atom of thioamides (1) to yield S-alkylthioimidolium salts (2) which can be deprotonated to form thioimidates (3).[4] Only from that limited range of alkylating agents which form stable carbocations, such as triphenylmethyl chloride or xanthydryl alcohol, can the products (5) of N-alkylation be obtained.[2] It was pointed out by Hurd[5] that such N-alkylation is a result of the reversibility of reaction 1⇌2 in such cases, because gradual reaction via (4) can then proceed to form the thermodynamically more stable product (5). This interpretation is supported by further work,[6,7] and by the fact that thioamides give N-substitution products on aminoalkylation,[8] hydroxyalkylation,[9] and alkoxyalkylation,[10] which are all thermodynamically controlled reactions.



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Our group has shown that the readily available[11] products 8 of the aminoalkylation of benzotriazole 6 are reduced in high yield[12] to the N-alkylarylamines 9 (including the possibility of N-alkylation of heteroarylamines such as 2-aminopyridine and adenine). Recently, this methodology has been extended to develop a method for N-alkylation of amides.[1] We now report a further extension which provides for the first time a general method for the N-alkylation of thioamides.

A variety of aldehydes, when treated with thiobenzamide, thiourea or thioisonicotinamide in toluene, in the presence of a mole of benzotriazole, readily yield adducts 10 by the loss of water removed (azeotropically). Details are listed in Table 1. Compounds of the type 8 exist in solution[13] as a mixture of rapidly interconverting 1- and 2-isomers with the 1- substituted

compound predominant. In our case the two isomers have been found for the compounds (10j-l), when thioisonicotinamide has been used. The two isomers can be separated using column chromatography. Our crystalline adducts 10(a-i) are all 1-isomers (10) without the 2-isomer (11) and, as is proved by the ^{13}C-NMR spectra, there is no rapid 10 ⇌ 11 equilibrium in solution. It is expected that isomerization would be slower here.[14] The oily thioisonicotinamide adducts (10j-l) after succesful separation were fully characterized by their analytical and spectral properties. The structures of the corresponding 2-isomers (11) were determined from the spectroscopic data.

The adducts were reduced by $NaBH_4$ in refluxing THF to give the expected N-substituted thioamides (12) as documented in Table 3.

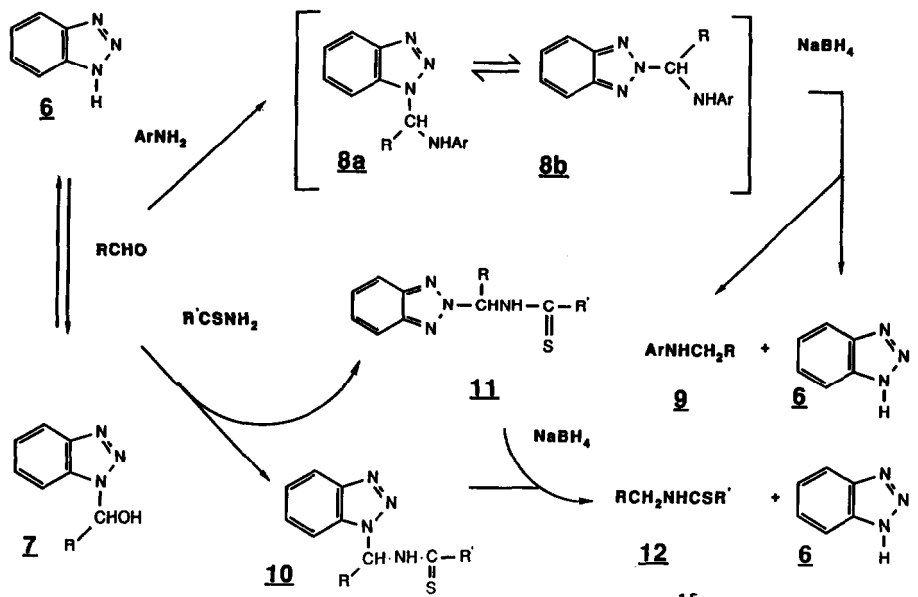

Table 1. Preparation of N-[1-(benzotriazol-1-yl)alkyl]thioamides 10.[15]

Product No	R of RCHO	R^1 of R^1CSNH_2	Time (h)	Yield (%)	Recryst. solvent	M.p. (°C)	Crystal Form
10a	H	Ph	9	53	Benzene/EtOH (1:4)	203-206	Needles
10b	i-Pr	Ph	48	48	Benzene	193-195	Needles
10c	n-Pr	Ph	27	71	Benzene	160-164	Prisms
10d	n-Pent	Ph	6	44	Benzene	145-148	Plates
10e	n-Heptyl	Ph	9	62	Ethanol	134-136	Needles
10f	n-Oct	Ph	5	67	Benzene	138-143	Plates
10g	n-Undec	Ph	24	45	Ethanol	117-120	Microcryst.
10h	i-Pr	NH_2	48	46	Acetone	199-200	Needles
10i	n-Heptyl	NH_2	20	35	Acetone	178-180	Needles
10j	n-Pent	4-Py	6	48	a		Oil
10k	n-Heptyl	4-Py	24	85	a		Oil
10l	n-Nonyl	4-Py	24	75	a		Oil

[a]See elemental analysis

Table 2. ^{13}C NMR chemical shifts[a-c] of the benzotriazole and R^1 carbons in 10 and 11.

Product	C=X	$NHCH_nR^1$	C-1′	C-2′	C-3′	C-4′	C-3a	C-4	C-5	C-6	C-7	C-7a
10a	199.6	55.5	139.3	126.7	126.3	130.0	144.3	118.0	122.9	126.7	109.9	131.4
10b	201.1	73.8	140.8	127.9	127.5	131.1	144.7	119.2	124.0	127.4	111.2	132.9
10c	199.9	67.1	139.9	126.7	126.6	129.9	144.2	118.2	122.9	126.5	109.9	131.6
10d	200.4	67.5	140.6	128.2	127.1	131.5	145.1	119.3	124.4	127.8	110.6	133.2
10e	200.5	68.6	140.7	127.9	127.4	131.2	145.0	119.2	124.1	127.5	111.0	132.3
10f	200.4	68.4	140.7	127.7	127.5	131.0	145.0	119.1	123.9	127.2	110.9	132.2
10g	200.4	67.6	140.5	128.1	127.2	131.4	145.0	119.1	124.3	127.7	110.7	133.1
10h	183.8	73.0	-	-	-	-	144.7	118.9	123.8	127.1	111.2	132.7
10i	183.6	67.3	-	-	-	-	145.0	119.1	124.0	127.2	110.8	132.3
10j	198.1	67.5	147.7	121.2	149.5	-	145.0	119.3	124.6	128.0	110.5	133.2
10k	198.0	67.5	147.7	121.2	149.1	-	144.9	119.1	124.4	127.8	110.4	133.1
10l	198.0	67.5	147.6	121.2	149.5	-	145.0	119.3	124.6	128.0	110.5	133.2
11j	197.6	74.5	147.7	120.6	150.2	-	144.1	118.4	127.0	127.0	118.4	144.1
11k	197.9	74.5	148.1	121.1	149.3	-	143.9	118.2	126.8	126.8	118.2	143.9
11l	197.9	74.5	148.1	121.1	149.2	-	143.9	118.9	126.7	126.7	118.9	143.9

[a]All spectra were run on XL 200 (FT mode,50 MHz) [b]All spectra were run in $CDCl_3$ except for 10(a-f) that were run in DMSO-d_6 [c]Chemical shifts of the carbons in the R substituents for compounds 10(b-l) and 11(j-l) were as expected.

Table 3. Preparation of N-alkylthioamides 12[a,b] RCH_2NHCSR^1

Product No	R of RCHO	R^1 of R^1CSNHR	Yield (%)	Recryst. solvent	M.p. °C	Lit.M.p. °C	Physical form
12a	H	Ph	98	Ethanol	77-80	79-80[16]	Microcrystals
12b	i-Pr	Ph	99		-	-	Oil[c]
12d	n-Pent	Ph	92	-	-	-	Oil[d]
12e	n-Heptyl	Ph	95	-	-	-	Oil[e]
12f	n-Oct	Ph	97	-	-	-	Oil[f]
12h	i-Pr	NH_2	60	Water	99-101	100-101[17]	Prisms
12i	n-Heptyl	NH_2	60	Pet.Ether/EtOH	98	96-97[18]	Plates

[a]All spectra were run on XL 200 (FT mode, 50 MHz) instrument in $CDCl_3$ [b]Chemical shifts of the carbons in compounds 12(a-i) : 12a 199.4, 141.0, 128.1, 126.4, 130.7, 33.3; 12b 197.3, 140.9, 127.7, 126.2, 130.6, 53.4, 26.8, 19.9; 12d 198.4, 141.4, 127.9, 126.4, 130.5, 46.5, 31.1, 27.6, 26.4, 22.2, 13.7; 12e 198.7, 141.7, 128.2, 126.5, 130.9, 46.7, 31.6, 29.1, 29.0, 27.9, 26.9, 22.4, 13.9; 12f 198.5, 141.4, 127.9, 126.4, 130.5, 46.6, 31.5, 29.2, 29.0, 27.7, 26.8, 22.3, 13.8; 12h 183.3, 51.5, 27.7, 20.0, 19.95; 12i 181.0, 44.3, 31.5, 29.0, 26.6, 24.3, 22.4, 12.6. [c]MS: for $C_{11}H_{15}NS$ calculated 193.0925, found 193.0922 [d]MS: for$C_{13}H_{19}NS$ calculated 221.1238, found 221.1235 [e]b.p. 194-198°C/2mmHg Lit. b.p.[19] 196-197°C/2mmHg [f]MS: for $C_{16}H_{25}NS$ calculated 263.1707, found 263.1677.

Experimental: Typical experimental procedure for preparation of the adducts 10:
Equimolar amounts (0.1mole) of benzotriazole, thioamide and aldehyde were suspended in 40 ml of anhydrous toluene and refluxed using Dean-Stark adapter for the appropriate time (see Table 1). The water was collected (theory 1.8ml) and the solvent was removed (60°C/25mmHg). The residue was recrystallized from the appropriate solvent. For the preparation of 10a, 1-hydroxybenzotriazole[20] was used in place of benzotriazole and formaldehyde. For the preparation of 10h and 10i two equivalents of thiourea were used.

Typical experimental procedure for reduction of 10 to 12:
3 mmoles of the adduct (10) were taken up in 30 ml of dry THF and 3 mmoles of solid sodium borohydride was added in one portion at room temperature. After 30 min of reflux, the solvent was removed (30/25mmHg); the residue was treated with 30 ml of water and extracted with chloroform (3 x 30 ml). The organic layer was washed with 2N NaOH (30 ml), water (30 ml) and dried with $MgSO_4$ (10g). Evaporation of the solvent (25°C/25mmHg) yielded the N-alkylthioamides (Table 2).

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