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α-(Benzotriazolyl)methyl Phenyl Thioethers: Convenient Reagents for α-Phenylthioalkylation of Silylated Nucleophiles

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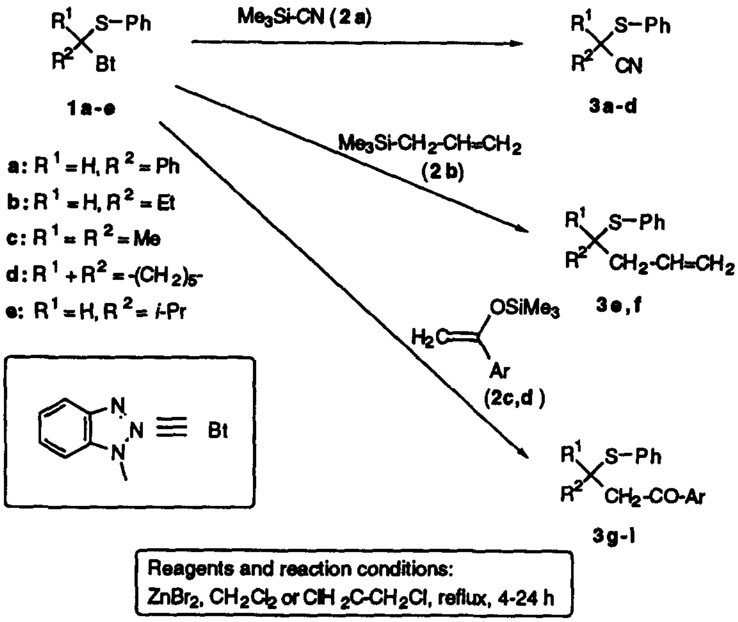
Abstract: Stable, crystalline α-(benzotriazolyl)methyl phenyl thioethers (1), easily prepared from carbonyl compounds, thiophenol and benzotriazole, are convenient reagents for the phenylthiomethylation of trimethylsilyl cyanide, trimethylallylsilane, and trimethylsilyl enol ethers to afford the corresponding substituted thioethers and β-phenylthioalkylketones (3) in good yields.

Kraus and *Maeda* [1] have recently proposed α-acetoxy sulfides of type R^1-CH(OAc)-SR for the Lewis acid catalyzed α-phenylthioalkylation of ketones (as *O*-silylated enolates), allyl silanes, and silyl cyanide. As stated by these authors,[1] this procedure is usually more convenient than earlier α-phenylthioalkylation methods employing α-chloromethyl aryl sulfides R^1-CH(Cl)-SR[2-8] (which have to be prepared from the corresponding methyl aryl sulfides by chlorination[9]). Other reagents described in the literature are α-tributylstannyl sulfides (made from benzyl sulfides by deprotonation and reaction with Bu_3SnCl[10]), and α-nitro sulfides (derived from nitro compounds by sulfenylation or by alkylation of α-phenylthionitromethane[11]).

α-Alkylthioalkylation has considerable synthetic utility because of the ease of conversion of the products into α-methylene-ketones or -lactones, key intermediates for the preparation of various sesquiterpenes and antibiotics.[2,3] Additionally, as shown by *Sato et al.*, allylated sulfides are valuable building blocks in the preparation of the synthetic analogs of various pheromones.[12] (For a review of the α-phenylthioalkylation of silylated nucleophiles, see ref.[13]). However, the new methodology[1] has some drawbacks. Thus, the procedure of *Kraus* and *Maeda* used mercury diacetate in the preparation of α-acetoxy sulfides; moreover, α-acetoxy sulfides are unstable and readily revert back to thioacetals on silica gel during attempted purification.[1]

We have now found that the use of α-(benzotriazolyl)methyl thioethers instead of α-acetoxy sulfides in this methodology offers a valuable alternative. Thioethers **1a-e** were all easily prepared as previously described[14] from the corresponding carbonyl compound, thiol and benzotriazole. Compounds **1a-d** were shown to react readily with trimethylsilyl-containing nucleophiles in the presence of the mild Lewis acid $ZnBr_2$ to give the desired α-substituted thioethers in good yields (Scheme 1, Table).

The reaction of trimethylsilyl cyanide **2a** with the four α-benzotriazolyl phenyl sulfides **1a-d** gave the desired α-cyano(cyclo)alkyl phenyl sulfides **3a-d** in the yields of 48-81%. Allyltrimethylsilane **2b** reacted with benzotriazolyl derivatives **1a** and **1b** to afford the expected α-substituted but-3-en-1-yl phenyl sulfides **3e** and



Scheme 1

Table. Preparation of Phenyl Thioethers 3a-i

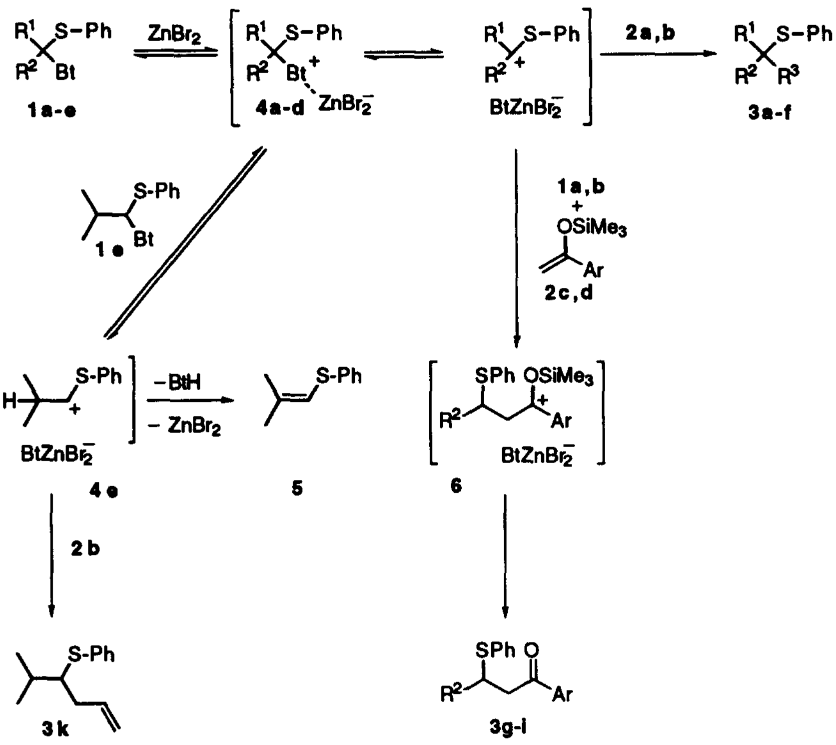
	$R^1R^2R^3C$-S-Ph				Reaction	Yield,	
3	R^1	R^2	R^3	Solvent	time, h	% [a]	Appearance
a	H	Ph	CN	CH_2Cl_2	24	81	plates; mp 49-50 °C (lit,[15] 48-49 °C)
b	H	Et	CN	$(CHCl_2)_2$	18	43	oil
c	Me	Me	CN	CH_2Cl_2	18	58	oil
d	$-(CH_2)_5-$		CN	CH_2Cl_2	18	42	oil
e	H	Ph	$-CH_2-CH=CH_2$	CH_2Cl_2	18	85	oil[b]
f	H	Et	$-CH_2-CH=CH_2$	$(CHCl_2)_2$	4	60	oil
g	H	Ph	$-CH_2$-CO-Ph	CH_2Cl_2	24	83	plates;[b] mp 119-120 °C (lit,[10] 114-115 °C)
h	H	Ph	$-CH_2$-CO-C_6H_4Me-p	CH_2Cl_2	18[c]	83	needles; mp 131-132 °C
i	H	Et	$-CH_2$-CO-Ph	$(CHCl_2)_2$	18	48[d]	oil

[a] After purification; all new compounds gave C,H,N and/or HRMS data within acceptable limits

[b] The NMR data of this compound are consistent with those published previously[10]

[c] Reaction was carried out at room temperature

[d] Crude reaction product was twice distilled (Kugelrohr; b.p. 125-128 °C/0.08 Torr)



Scheme 2

3f, respectively (60 and 85%). The silylated enols **2c** and **2d** underwent the anticipated reactions to yield the β-substituted-β-(phenylthio)ethyl aryl ketones **3g**, **3h** and **3i** (48-83%). Of the products now synthesized, three are novel (**3c,h,i**). The other six were previously reported, being prepared using less convenient and/or less available precursors: (i) α-chloroethyl phenyl sulfide for **3a**,[15] (ii) α-(tributylstannyl)alkyl sulfides for **3g,e**,[10] (iii) α-nitro sulfides for **3b,f**,[11] and (iv) an alkenyl sulfide for **3d**.[16]

The mechanism of these reactions probably involves the formation from **1a-e** of the thionium cation complexes **4a-e** with zinc bromide, which upon nucleophilic attack of either silyl cyanide (**2a**) or allyl silane (**2b**) gives the corresponding thioethers **3a-f** (Scheme 2). Addition of enol ethers **2c,d** to complexes of type **4a-d** first gives an ionized intermediate **6**, which again *via* elimination forms ketone thioethers **3g-i**. Results of the reaction of 1-(benzotriazol-1-yl)-1-phenylthio-2-methylpropane (**1e**) with allyl trimethyl silane (**2b**) supported the suggested mechanism: the NMR and GC/MS spectra of the crude reaction product revealed the presence of the mixture of allyl thioether **3k** and vinyl sulfide **5** in a ratio of *ca* 3:2. Formation of vinyl sulfide from the intermediate **4e** occurs *via* elimination of a benzotriazole molecule upon heating in the presence of an acid catalyst, thus competing with the main course of the reaction.

A typical preparation of phenyl thioethers **3a-i** is given.[17] Compounds **3a-i** were fully characterized by their NMR and elemental analysis data. As compared to the method of *Kraus* and *Maeda*,[1] the advantages of the new methodology include stability and convenience in the preparation and purification of the intermediate benzotriazole adducts **1a-d**. It also appears to be more general: we prepared the cyano cyclohexyl thioether (**3d**) *via* the stable crystalline intermediate **1d**, while the reaction of the dithioketal of cyclohexanone with mercuric acetate was reported[1] to give only the elimination product, cyclohexenyl ethyl sulfide.

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17. A mixture of adduct **1a-d** (5 mmol), silyl nucleophile **2a-d** (6 mmol), and anhydrous zinc bromide (6 mmol) in methylene chloride or 1,2-dichloroethane (20 mL) was refluxed for the time specified (Table). The precipitate formed was filtered off and washed with methylene chloride. The combined organics were washed with saturated aqueous Na_2CO_3, then with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The resulting crude products were purified by column chromatography (silica gel, eluent - hexanes for **3a,e,f**, and hexanes:CH_2Cl_2 (8:1) for **3b-d,i**) or recrystallized (**3g,h**, from ethyl acetate).

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