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

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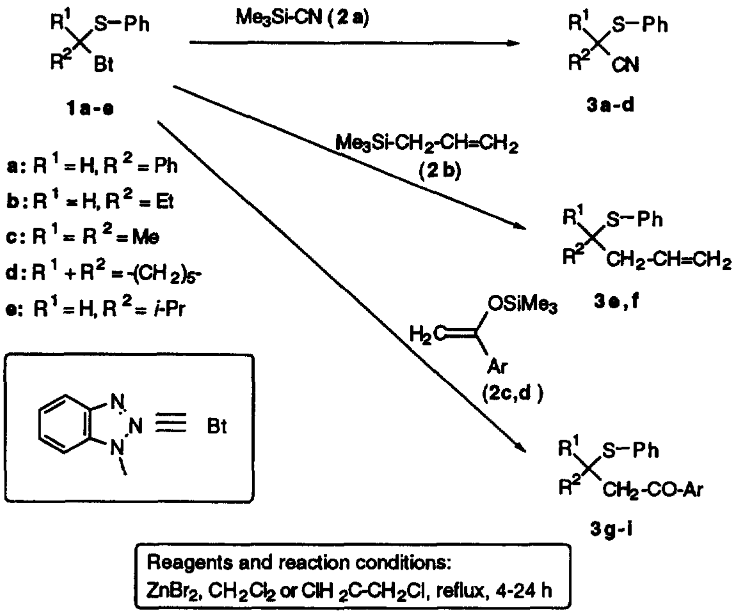
Abstract: Stable, crystalline α-(benzotriazolyl)methyl phenyl thioethers (**1**), easily prepared from carbonyl compounds, thiophenol and benzotriazole, are convenient reagents for the phenylthiomethylation of trimethylsilyl cyanide, trimethylallylsilane, and trimethylsilyl enol ethers to afford the 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[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

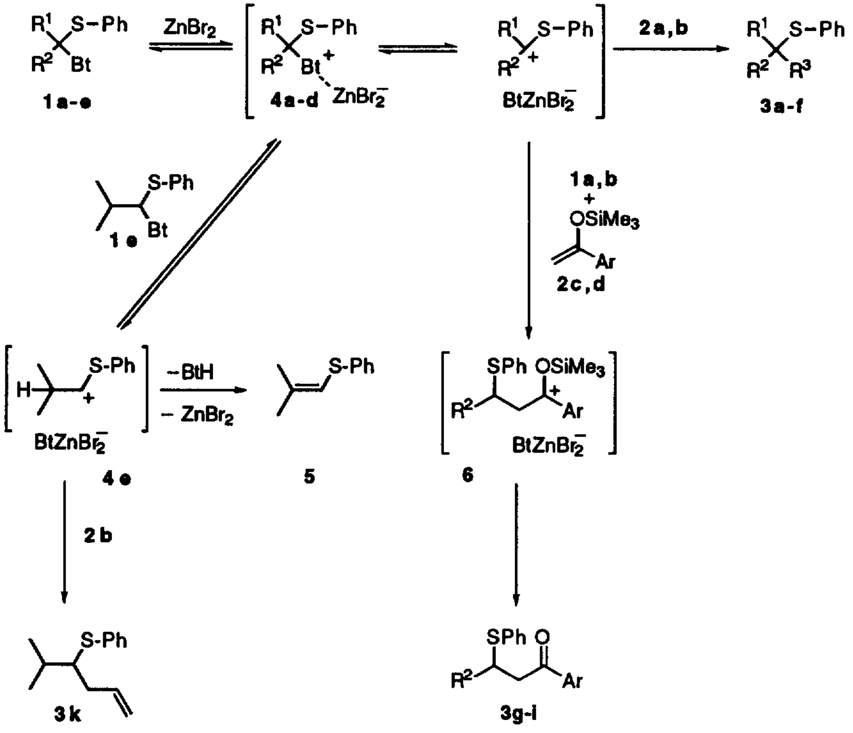
3	$R^1R^2R^3C$-S-Ph			Solvent	Reaction time, h	Yield, %[a]	Appearance
	R^1	R^2	R^3				
a	H	Ph	CN	CH_2Cl_2	24	81	plates; mp 49-50 °C (lit,[15] 48-49 °C)
b	H	Et	CN	$(CHCl_2)_2$	18	43	oil
c	Me	Me	CN	CH_2Cl_2	18	58	oil
d	$-(CH_2)_5-$		CN	CH_2Cl_2	18	42	oil
e	H	Ph	$-CH_2-CH=CH_2$	CH_2Cl_2	18	85	oil[b]
f	H	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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