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A CONVENIENT ROUTE TO β-PHENYLTHIOALKYL KETONES

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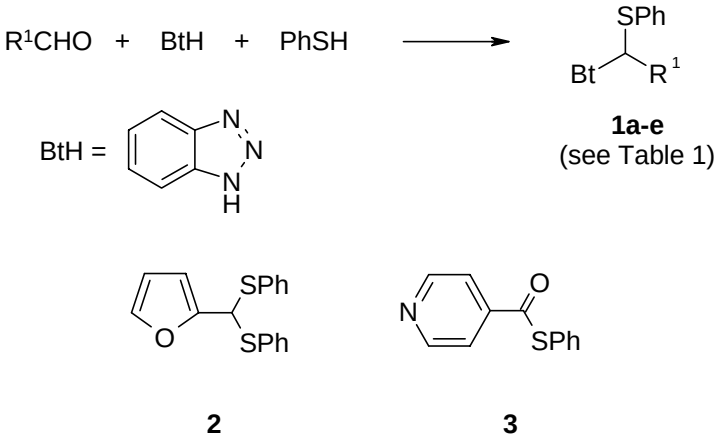
Abstract-The preparation of β-phenylthioalkyl ketones *via* the reactions of α-benzotriazolylalkyl phenyl sulfides (**1a-e**) with enamines (**5a-d**) is described.

β-Phenylthio ketones have considerable synthetic utility because of their ease of conversion into α-methylene ketones[1] and desulfurization.[2] Several strategies have been reported for the construction of β-phenylthio ketones: (A) from α,β-unsaturated ketones by the addition of (i) thiophenol,[3a-e] (ii) organoaluminium Me_2AlSPh,[4a,b] or (iii) lanthanoid thiolates;[5] (B) by reaction of silyl enol ethers with (i) α-chloroalkyl sulfides,[1, 2, 6a-d] (ii) thioacetals,[7] (iii) α-acetoxy sulfides,[8] (iv) alkenyl sulfides,[9] (v) γ-(phenylthio)allenylstannanes,[10] (vi) α-stannylbenzyl sulfides,[11] (vii) vinylthionium ions[12] or (viii) α-(benzotriazolyl)methyl thioethers;[13] (C) by pinacol rearrangement of sulfenylmethylated glycols;[14] (D) by treatment of α,β-epoxy sulfoxides with sodium benzeneselenolate;[15] (E) by rearrangement of epoxides bearing a proton β to an electron-withdrawing group in the presence of stoichiometric amount of PhSNa or a combination of PhSH and Et_3N;[16] (F) by ring expansion of *t*-butyldimethylsilyl ethers of 1-alkenylcycloalkanols upon successive treatment with PhSCl and $AgBF_4$.[17]

To the best of our knowledge, enamines have not previously been used as nucleophiles in the preparation of β-phenylthio ketones. We now report that enamines react as nucleophiles with α-(benzotriazolyl)alkyl thioethers (eg **1a-e**) to provide a convenient access to β-phenylthio ketones.

The preparation of starting materials (1a-e). Using methodology previously developed in our laboratories,[18] starting materials (**1a-e)** were prepared from the corresponding aldehydes (Table 1) in reasonable yields except for **1d** for which dithioacetal (**2**) (Scheme 1) was isolated as a major by-product (30%). Compounds (**1b-e**) are novel and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis (Table 1). When 4-pyridinecarboxaldehyde was used, thioester (**3**) and diphenyl disulfide were the major products instead of the desired thio ether.



Scheme 1

Table 1. The Preparation of α-(Benzotriazolyl)alkyl Thioethers (1a-e).

No.	R^1	mp (°C)	Yield (%)	CHN Found (Calcd)		
				C	H	N
1a	Ph	80-82	75	lit.,[18] mp 81-82 °C		
1b	*p*-CH_3OPh	109-111	73	69.52 (69.14)	5.31 (4.93)	11.67 (12.09)
1c	*p*-ClPh	77-79	57	64.96 (64.86)	3.65 (4.01)	11.99 (11.94)
1d	2-furyl	81-83	40	66.60 (66.43)	4.30 (4.26)	13.74 (13.67)
1e	*o*-ClPh	76-78	45	64.79 (64.85)	3.92 (4.02)	11.94 (11.94)

The preparation of β-phenylthio ketones (6a-f). Reactions of enamine (**5a**) with α-benzotriazolylalkyl phenyl sulfides (**1a,b**) provided the desired β-phenylthio ketones (**6a,b**) in 43% and 51% yields, respectively. In addition to the cyclohexanone-pyrrolidine enamine (**5a**), the morpholine enamine of diethyl ketone (**5b**) and the diethylenamine of propiophenone (**5c**) also gave satisfactory results, thus β-phenylthio ketones (**6c-f**) were obtained in moderate to good yields; however, an attempt to use the morpholine enamine of cyclopentanone failed. In the products, the R^1 group ranged from phenyl or

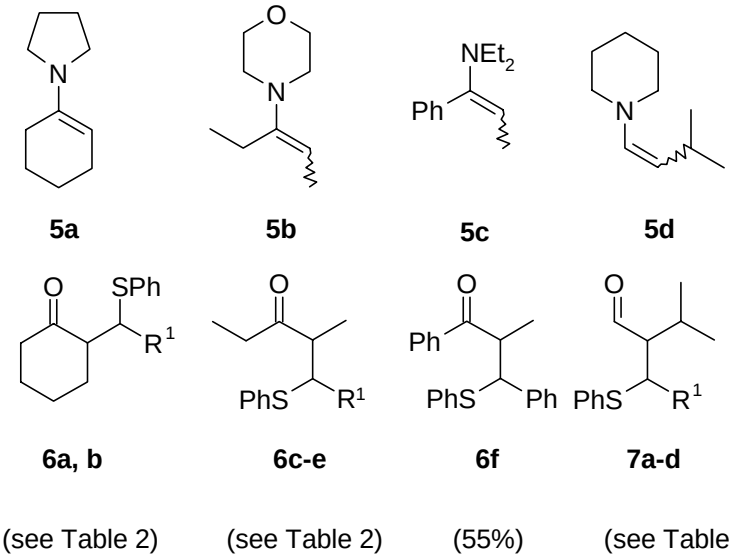
substituted phenyl (with an electron-withdrawing or electron-donating substituent) to a heterocyclic aryl group. The products (**6a-e**) now synthesized are novel. Product (**6f**) was previously prepared by the reaction of α-tributylstannylbenzyl sulfide with enol silyl ether with CAN or $[Fe(cp)_2]PF_6$ as oxidant.[11] Structures (**6a-f**) were supported by their ^1H and ^{13}C NMR spectra and by elemental analysis or high resolution MS data. The doublets on ^1H NMR around 5.4 ppm was assigned to the proton adjacent thiophenyl group. The peak on ^{13}C NMR around 212 ppm, which was assigned to the carbonyl carbon, also supported the structures. The expected two diastereoisomers for product (**6a-f**) were shown by two peaks of corresponding molecular weight in the GC/MS spectra. No attempts to separate these two isomers were made. In all these reactions, by-products from elimination of the phenylthio group were observed: in the reaction of **1d** with acyclic enamine (**5b**), 30% of the α,β-unsaturated ketone was obtained. The piperidine enamine (**5d**), derived from isovaleraldehyde, reacted with α-benzotriazolylalkyl phenyl sulfides (**1a,c-e**) to give the desired products (**7a-d**). Among of them, **7a** and **7c** were mixed with 30 – 35% of α,β-unsaturated aldehyde elimination products shown by their NMR spectra and can not be isolated as pure products.

Table 2. The Preparation of β-Phenylthioalkyl Ketones (6a-f) and β-Phenylthioalkyl Aldehydes (7a-d).

Starting	Enamine	Product			CHN Found (Calcd) or HRMS found (Calcd)	
Bt-compd		No.	R^1	Yield(%).	C	H
1a	**5a**	**6a**	Ph	43	76.68 (76.99)	7.13 (6.81)
1b	**5a**	**6b**	*p*-CH_3OPh	51	73.44 (73.58)	7.23 (6.79)
1a	**5b**	**6c**	Ph	69	76.08 (76.01)	7.39 (7.09)
1c	**5b**	**6d**	*p*-ClPh	55	318.0841 (318.0845)	
1d	**5b**	**6e**	2-furyl	40	70.34 (70.04)	6.40 (6.61)
1a	**5c**	**6f**	Ph	55		
1a	**5d**	**7a***	Ph	41	Yield was determined by GC/MS	
1c	**5d**	**7b**	*p*-ClPh	50	67.96 (67.80)	6.32 (6.02)
1d	**5d**	**7c***	2-furyl	35	Yield was determined by GC/MS	
1e	**5d**	**7d**	*o*-ClPh	40	67.72 (67.80)	6.38 (6.02)

*As mixture with α,β-unsaturated aldehyde.

In conclusion, β-phenylthioalkyl ketones (**6a-f**) and β-phenylthioalkyl aldehydes (**7a-d**) were prepared under mild conditions from enamines using stable and easily prepared benzotriazole intermediates by the selective cleavage of a C-N bond in the presence of a C-S bond. The familiar method of preparing β-phenylthioalkyl ketones from olefin and PhSH appears to be restricted to addition to terminal or cyclic C=C bonds. However, our method can lead to a variety of types difficult to prepare by previous methods.



Scheme 2

EXPERIMENTAL

General Comments. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini-300 spectrometer in $CDCl_3$ with TMS or $CDCl_3$, respectively, as the internal reference. Column chromatography was carried out on MCB silica gel (230-400 mesh). Methylene chloride was freshly distilled from phosphorus pentoxide.

General Procedure for the Preparation of β-Phenylthioalkyl Ketones (**6a-f**): Zinc bromide (0.45 g, 2 mmol) was added to the solution of α-benzotriazolylalkyl phenyl sulfides (**1a-d**) (2 mmol) in 15 mL methylene chloride and the mixture was refluxed with stirring under nitrogen for 2 h. Enamine (**5a-c**) (4.0 mmol) was added in one portion to the mixture and was heated at reflux for additional 20 h. The reaction mixture was then cooled to ambient temperature and washed with saturated aqueous solution of sodium carbonate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0.5% ethyl acetate in hexanes) furnished the β-phenylthioalkyl ketone (**6a-f**).

1-[(1-Phenylthio)benzyl]-1*H*-benzotriazole (**1a**): mp 80-82 °C. ^{1}H NMR δ: 8.03 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57-7.19 (m, 7H), 7.18-7.05 (m, 5H); ^{13}C NMR δ: 146.7, 135.5, 133.4, 131.6, 131.3, 129.2, 129.0, 128.9, 127.2, 126.9, 124.0, 120.2, 111.8, 70.5.

1-[(4-Methoxyphenyl)phenylthiomethyl]-1*H*-benzotriazole (**1b**): mp 109-111 °C. ^{1}H NMR δ: 8.02 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.50-7.30 (m, 5H), 7.27-7.06 (m, 5H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR δ: 160.0, 146.7, 133.3, 131.6, 131.4, 129.1, 128.8, 128.3, 127.6, 127.2, 124.0, 120.2, 114.2, 111.8, 70.1, 55.3.

1-[(4-Chlorophenyl)phenylthiomethyl]-1*H*-benzotriazole (**1c**): mp 77-79 °C. ^{1}H NMR δ: 8.03 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.48-7.24 (m, 7H), 7.23-7.04 (m, 5H); ^{13}C NMR δ: 146.6, 135.0, 134.0, 133.4, 131.5, 130.8, 129.2, 129.0, 128.3, 127.4, 124.1, 120.2, 111.5, 69.7.

2-[(1-Benzotriazol-1-yl-1-phenylthio)methyl]furan (**1d**): mp 81-83 °C. ^{1}H NMR δ: 7.81 (d, *J* = 8.4 Hz, 1H), 7.52-7.30 (m, 4H), 7.29-7.06 (m, 5H), 6.62-6.56 (m, 1H), 6.42-6.37 9m, 1H); ^{13}C NMR δ: 147.6, 146.7, 143.6, 133.8, 131.4, 130.5, 129.3, 129.2, 127.4, 124.1, 120.1, 111.9, 110.8, 110.0, 64.1.

1-[1-(2-Chlorophenyl)-2-phenylthio]-1*H*-benzotriazole (**1e**): mp 76-78 °C. ^{1}H NMR δ: 8.03 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.48-7.38 (m, 2H), 7.35-7.25 (m, 5H), 7.24-7.10 (m, 3H); ^{13}C NMR δ: 146.0, 133.8, 133.7, 132.8, 132.5, 131.5, 130.4, 129.9, 129.2, 129.1, 127.5, 124.0, 120.1, 110.4, 66.6.

2-[Phenyl(phenylthio)methyl]cyclohexanone (**6a**): Oil. ^{1}H NMR δ: 7.35-7.05 (m, 10H), 4.69 (d, *J* = 7.9 Hz, 1H), 2.95-2.82 (m, 1H), 2.58-2.25 (m, 2H), 2.02-1.50 (m, 5H), 1.45-1.25 (m, 1H); ^{13}C NMR δ: 210.6, 139.8, 134.9, 132.2, 128.9, 128.6, 128.1, 127.1, 55.8, 51.9, 41.8, 31.7, 28.1, 24.2.

2-{(4-Methoxyphenyl)(phenylthio)methyl]cyclohexanone (**6b**): Oil. ^{1}H NMR δ: 7.30-7.10 (m, 7H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.68 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 2.91-2.78 (m, 1H), 2.55-2.27 (m, 2H), 2.04-1.89 (m, 2H), 1.88-1.51 (m, 3H), 1.46-1.26 (m, 1H); ^{13}C NMR δ: 210.7, 158.5, 135.0, 132.1, 131.6, 129.9, 128.6, 126.9, 113.4, 55.9, 55.1, 51.2, 41.7, 31.4, 27.9, 24.1.

2-Methyl-1-phenyl-1-phenylthio-3-pentanone (**6c**): Oil. (mixture of two isomers). ^{1}H NMR δ: 7.35-7.03 (m, 10H), 4.37 (4.27) (d, *J* = 10.7 Hz, 1H), 3.18-3.03 (m, 1H), 2.64 (q, *J* = 7.1 Hz, 1H), 2.40-2.22 (2.10-

1.98) (m, 1H), 1.38 (0.86) (d, *J* = 6.9 Hz, 3H), 0.76 (1.13) (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ: 213.0 (212.6), 141.1 (140.3), 132.6 (134.2), 132.5, 128.6, 128.2, 128.1, 128.0, 127.3, 127.1, 127.0, 56.8 (56.1), 51.8 (50.7), 36.0 (36.4), 15.9 (16.4), 7.3 (7.6).

1-(4-Chlorophenyl)-2-methyl-1-phenylthio-3-pentanone (**6d**): Oil. (mixture of two isomers). ^{1}H NMR δ: 7.31-7.03 (m, 9H), 4.25 (4.34) (d, *J* = 10.7 Hz, 1H), 3.14-2.97 (m, 1H), 2.65 (q, *J* = 7.2 Hz, 1H), 2.45-2.27 (2.10-1.95) (m, 1H), 0.86 (1.40) (d, *J* = 7.0 Hz, 1H), 1.14 (0.81) (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ: 212.7 (211.7), 139.0 (140.0), 133.7 (131.0), 132.9, 129.6 (129.4), 128.7 (128.6), 128.5 (128.3), 127.7 (127.5), 55.6 (56.1), 50.5 (51.6), 36.1 (36.6), 16.4 (16.1), 7.6 (7.3).

1-(2-Furyl)-2-methyl-1-phenylthio-3-pentanone (**6e**): Oil. ^{1}H NMR δ: 7.44-7.14 (m, 6H), 6.26-6.13 (m, 1H), 5.90 (d, *J* = 2.8 Hz, 1H), 4.41 (d, *J* = 9.6 Hz, 1H), 3.28-3.12 (m, 1H), 2.52-2.18 (m, 2H), 1.38 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ: 212.4, 153.2, 141.7, 133.5, 128.7, 127.8, 110.2, 107.9, 49.7, 48.9, 35.1, 15.6, 7.5.

2-Methyl-1,3-diphenyl-3-phenylthio-1-propanone (**6f**): Oil. (mixture of two isomers). ^{1}H NMR δ: 7.76 (8.04) (d, *J* = 7.4 Hz, 2H), 7.65-7.31 (m, 3H), 7.30-6.96 (m, 10H), 4.60 (4.55) (d, *J* = 13.2 Hz, 1H), 4.18-3.98 (m, 1H), 1.54 (1.00) (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ: 204.7 (202.1), 141.4 (140.8), 136.4 (137.5), 133.2 (134.1), 132.9 (132.8), 128.6 (128.7), 128.5 (128.4), 128.3 (128.1), 128.0, 127.9, 127.2 (127.3), 126.9, 57.0 (56.4), 46.4 (45.5), 17.2 (17.1).

2-[(4-Chlorophenyl)phenylthiomethyl]-3-methylbutanal (**7b**): Oil. ^{1}H NMR δ: 9.54 (s, 1H), 7.50-7.38 (m, 2H), 7.38-7.25 (m, 2H), 7.25-7.10 (m, 4H), 7.10-6.98 (m, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 3.20-3.00 (m, 1H), 2.85-2.50 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR δ: 195.3, 148.4, 147.9, 134.0, 130.3, 129.7, 128.9, 128.5, 128.1, 76.6, 26.9, 20.3, 17.4.

2-[(2-Chlorophenyl)phenylthiomethyl]-3-methylbutanal (**7d**): Oil. (mixture of two isomers). ^{1}H NMR δ: 9.86 (9.49) (d, *J* = 4.5 Hz, 1H), 7.33-7.10 (m, 9H), 5.25-5.08 (m, 1H), 2.80-2.60 (m, 1H), 1.85-1.70 (m, 1H), 1.00 (1.14) (d, J = 6.9 Hz, 3H), 0.94 (1.12) (d, J = 7.0 Hz, 3H); ^{13}C NMR δ: 203.0, 133.7 (133.6), 129.6, 128.8, 128.7, 128.5, 128.1, 127.0, 76.5, 29.1 (28.7), 21.4 (21.6), 17.7 (17.1).

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