AROMATIC ANNULATIONS *VIA* BENZOTRIAZOL-1-YL-PHENYLTHIOMETHANE AS A 1,1-DIPOLE SYNTHON EQUIVALENT

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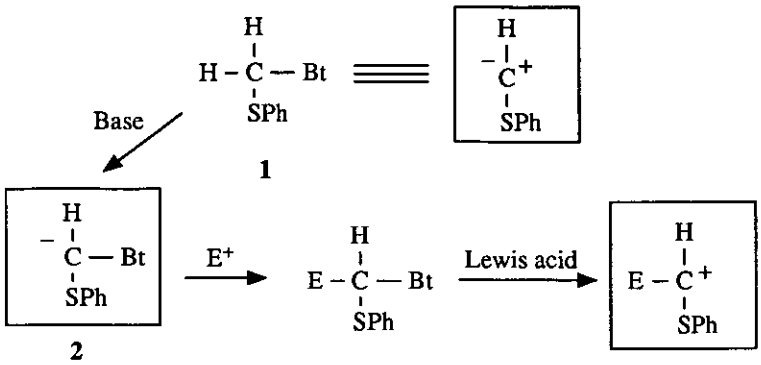
Abstract - The title compound readily deprotonates and reacts with appropriate electrophiles to form derivatives which upon subsequent treatment with Lewis acids undergo ring closure to afford fused aromatics.

INTRODUCTION

Development of new synthetic approaches which result in the annulation of carbocyclic derivatives incorporating latent functionality has gained increased attention due to their potential application in the synthesis of complex organic compounds.[1-4] Recently, aromatic annulations mediated by 1,3-benzodithiolium and naphtho[1,8-*de*]-1,3-dithiin carbocations have been reported.[5,6] In both cases, a carbonyl group was liberated after acidic hydrolysis of the cyclization products. Work in our laboratory has demonstrated that the benzotriazolyl group in the compounds BtCH(R)X (where X = NR^1R^2, $NHCOR^3$, or SPh) can be removed under Lewis acid catalyzed conditions to afford the corresponding carbocations.[7-9] Trapping these cations with electron-rich aromatics or C-H acids *in situ* produces the corresponding amino-, amido- or thio-alkylated products in good yields. Benzotriazol-1-ylphenylthiomethane (**1**) has been shown to undergo deprotonation with butyllithium to afford a carbanion which reacts with a variety of electrophiles.[10] The ease with which the carbanion can be generated together with the facile removal of the benzotriazolyl group to form a carbocation initiated an investigation into the participation of this species as a 1,1-dipole synthon equivalent in aromatic annulations (Scheme 1).



Bt = Benzotriazol-1-yl

Scheme 1

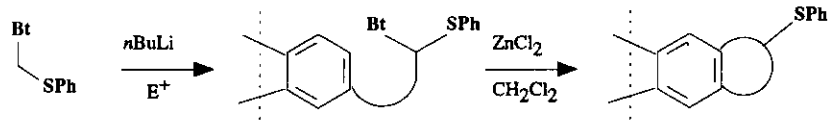
RESULTS AND DISCUSSION

Treatment of benzotriazol-1-ylphenylthiomethane (**1**) with butyllithium in THF at -78 °C for 1 h produced carbanion (**2**) which was then reacted with 1-bromo-3-phenylpropane to yield the intermediate product (**3a**) in 89% yield (Table 1). Treatment of this with aluminium chloride as the Lewis acid gave complex mixtures even under mild conditions (methylene chloride, 15°C, 10 min). With zinc chloride as the catalyst, the expected cyclization product (**4a**) was obtained in a yield of 92% after 12 h in refluxing methylene chloride. The liberated benzotriazole was easily removed by extraction with dilute aqueous sodium hydroxide. The structure of **4a** was confirmed by ^{1}H and ^{13}C nmr and its high resolution mass spectral data.

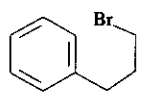
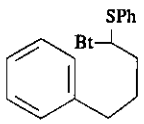
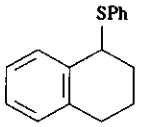
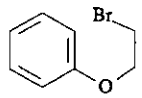
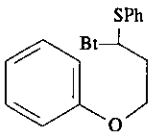
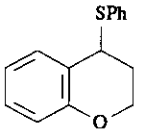
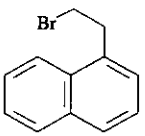
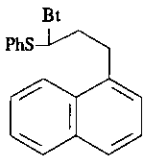
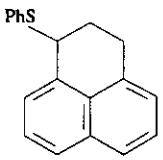
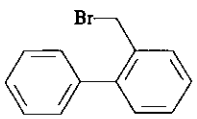
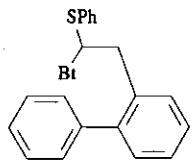
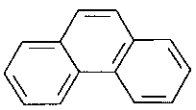
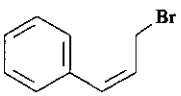
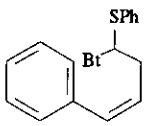
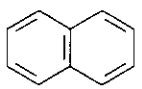
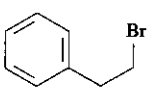
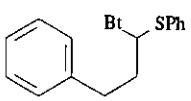
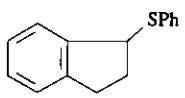
Considering the prevalence of oxygen heteroatoms in the carbon skeletons of some natural products, we were interested in the effect of an oxygen atom in the intervening chain. Thus, alkylation of anion (**2**) with β-bromophenetole under similar conditions, produced the requisite intermediate (**3b**) in 84% yield. Treatment of **3b** with two equivalents of zinc chloride resulted in the desired cyclization product (**4b**) in a yield of 87%.

Variation of the aromatic nucleus was briefly examined. Reaction of anion (**2**) with 2-(1-naphthyl)ethyl bromide produced the alkylated product (**3c**) (79%). Subsequent cyclization could give rise to either the five or six-membered ring product. Treatment of **3c** with zinc chloride in methylene chloride resulted in the exclusive formation of the six-membered ring compound (**4c**), presumably because geometric constraints disfavored a 5-*endo-trig* cyclization. The structure of **4c** was confirmed by ^{1}H and ^{13}C nmr and its high resolution mass spectral data.

Table 1. Reaction of benzotriazol-1-ylphenylthiomethane with butyllithium and electrophiles and subsequent cylizations



1 **3** **4**

Electrophile	Alkylated Product		Cyclized Product	
	Structure	Yield (%)	Structure	Yield (%)
	**3a** 	(89)	**4a** 	(92)
	**3b** 	(84)	**4b** 	(87)
	**3c** 	(79)	**4c** 	(69)
	**3d** 	(91)	**4d** 	(95)
	**3e** 	(89)	**4e** 	(87)
	**3f** 	(68)	**4f** 	(52)

To assess the phenylthio group's stability in a pro-aromatic environment, the cyclization of compound (**3d**), (obtained from reaction of anion (**2**) with 2-bromomethylbiphenyl), was carried out with zinc chloride in methylene chloride. After refluxing for 12 h, phenanthrene (**4d**) was the only isolated product. Shorter reaction time did not afford the expected cyclization product, instead, a mixture of **3d** and **4d** was observed. Presumably the ensuing aromaticity was the driving force for this behavior. A similar result was observed in the cyclization of compound (**3e**) obtained from the reaction of anion (**2**) with cinnamyl bromide, to afford naphthalene (**4e**) (87%).

Extension of this methodology to include a five-membered annulation has been successful. Alkylation of anion (**2**) with 2-phenylethyl bromide produced the intermediate (**3f**) in 68% yield. While slower than the cyclization of **3a**, **3f** was indeed converted to the expected 1-phenylthioindan (**4f**) in a yield of 52% after a longer period of reflux (ca. 24 h).

CONCLUSION

The ability of benzotriazol-1-ylphenylthiomethane to behave as a 1,1-dipole synthon equivalent and to enable aromatic annulations extends the application of benzotriazole derivatives in organic synthesis. The merit of this methodology relies on the simple synthetic availability and suitable reactivity of the title compound, as well as the mild reaction conditions employed in these cyclization procedures in the absence of activating groups on the aromatic nucleus. The resistance of the phenylthio group to Lewis acid catalysed elimination and its subsequent presence in the cyclization products described herein provides further opportunities for synthetic elaborations.

EXPERIMENTAL

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H-Nmr spectra were recorded on a Varian VXR-300 spectrometer with TMS as internal reference. ^{13}C-Nmr spectra were recorded at 75 MHz on the same instrument using solvent peak ($CDCl_3$, δ = 77.0 ppm) as reference. Microanalyses were carried out using a Carlo Erba 1106 elemental analyser. High resolution mass spectrometry was carried out on a Finnegan Mat 95. The following compound was prepared by a known literature procedure: **Benzotriazol-1-ylphenylthiomethane (1)**, mp 79-80 °C, (lit.,[10] mp 80 °C).

Lithiation of Benzotriazol-1-ylphenylthiomethane and Reaction with Alkyl Halides. General Procedure:

Butyllithium (4.4 ml, 2.5 M in hexane, 11 mmol) was added to a solution of benzotriazol-1-ylphenylthiomethane (2.41 g, 10 mmol) in THF (60 ml) under argon at -78 °C. The solution was stirred at this temperature for 1 h, and an appropriate alkyl halide (11 mmol) in THF (10 ml) was added. The mixture was stirred at -78 °C for 2 h, and warmed to room temperature overnight. The mixture was poured into saturated aqueous NH_4Cl (30 ml), and the aqueous layer extracted with Et_2O (3 × 30 ml). The combined organic layers were washed with H_2O (1 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure to give an oily product, which was purified by column chromatography (silica gel, hexane/$CHCl_3$ = 2:1) to afford the pure products as pale yellow oils.

1-(Benzotriazol-1-yl)-4-phenyl-1-phenylthiobutane (3a): ^{1}H-Nmr δ: 8.01 (dd, 1H, J=1.1 Hz and 8.1 Hz), 7.63-7.58 (m, 1H), 7.43-7.00 (m, 12H), 6.14 (dd, 1H, J=6.4 Hz and 9.0 Hz), 2.68-2.34 (m, 4H), 1.82-1.68(m, 1H), and 1.60-1.47 (m, 1H). ^{13}C-Nmr δ: 146.3, 140.8, 133.4, 131.3, 130.9, 128.8, 128.5, 128.2, 128.1, 126.9, 125.8, 123.8, 119.9, 110.8, 67.4, 34.6, 33.4, and 27.9. HRms, *m/z* 360.1533 ($C_{22}H_{21}N_3S$ requires 360.1534).

Phenyl 3-(benzotriazol-1-yl)-3-phenylthiopropyl ether (3b): ^{1}H-Nmr δ: 8.01 (d, 1H, J=8.1 Hz), 7.50 (d, 1H, J=8.3 Hz), 7.41-7.30 (m, 2H), 7.28-7.16 (m, 3H), 7.14-7.07 (m, 4H), 6.97-6.78 (m, 3H), 6.42 (t, 1H, J=7.8 Hz), 4.20-4.12 (m, 1H), 3.90-3.81 (m, 1H), and 3.00-2.82 (m, 2H). ^{13}C-Nmr δ: 158.1, 146.1, 134.0, 131.9, 130.5, 129.3, 129.0, 128.9, 127.1, 124.0, 121.0, 120.0, 114.4, 110.5, 63.9, 63.6, and 34.0. HRms, *m/z* 362.1330 ($C_{21}H_{19}N_3OS$ requires 362.1328).

1-(Benzotriazol-1-yl)-3-(naphth-1-yl)-1-phenylthiopropane (3c): ^{1}H-Nmr δ: 8.03 (d, 1H, J=8.1 Hz), 7.84-7.68 (m, 3H), 7.52 (d, 1H, J=8.4 Hz), 7.58-7.29 (m, 5H), 7.24-7.00 (m, 6H), 6.20-6.14 (m, 1H), and 3.20-2.74 (m, 4H). ^{13}C-Nmr δ: 146.4, 135.4, 133.7, 133.6, 131.6, 131.3, 130.7, 128.9, 128.8, 128.7, 128.6, 127.1, 126.8, 126.0, 125.7, 125.3, 124.0, 123.2, 120.1, 110.9, 66.9, 34.9, and 29.7. *Anal.* Calcd for $C_{25}H_{21}N_3S$: C 75.92, H 5.35, N 10.62; Found: C 75.86, H 5.44, N 10.47.

2-[2-(Benzotriazol-1-yl)-2-phenylthioethyl]biphenyl (3d): ^{1}H-Nmr δ: 7.94-7.88 (m, 1H), 7.40-7.33 (m, 3H), 7.26-6.95 (m, 12H), 6.90-6.84 (m, 2H), 6.00 (t, 1H, J=8.0 Hz), and 3.81 (d, 2H, J=8.0 Hz). ^{13}C-Nmr δ: 145.9, 141.9, 140.6, 133.3, 132.9, 131.5, 131.2, 130.1, 130.0, 128.7, 128.6, 128.4, 128.3, 127.3, 127.2, 127.1, 126.7, 123.5, 119.7, 110.2, 67.5, and 38.1. HRms, *m/z* 408.1530 ($C_{26}H_{21}N_3S$ requires 408.1533).

4-(Benzotriazol-1-yl)-1-phenyl-4-phenylthiobut-1-ene (3e): ^{1}H-Nmr δ: 8.00 (d, 1H, J=8.3 Hz), 7.65 (d, 1H, J=8.2 Hz), 7.45-7.00 (m, 12H), 6.47-6.38 (m, 1H), 6.28-6.19 (m, 1H), 6.14-6.00 (m, 1H), and 3.41-3.22 (m, 2H). ^{13}C-Nmr δ: 146.3, 134.1, 133.6, 131.6, 130.7, 128.9, 128.8, 128.7, 128.3, 127.5, 127.0, 126.1, 123.9, 123.1, 120.0, 110.8, 67.1, and 37.8. *Anal.* Calcd for $C_{22}H_{19}N_3S$: C 73.92, H 5.36, N 11.75; Found: C 73.51, H 5.38, N 11.78.

1-(Benzotriazol-1-yl)-3-phenyl-1-phenylthiopropane (3f): ^{1}H-Nmr δ: 8.02 (d, 1H, J=8.1 Hz), 7.54 (d, 1H, J=9.3 Hz), 7.45-6.94 (m, 12H), 6.13-6.01 (m, 1H), and 2.90-2.57 (m, 4H). ^{13}C-Nmr δ: 146.3, 139.2, 133.5, 131.5, 130.7, 128.8, 128.7, 128.6, 128.4, 128.3, 127.0, 126.2, 119.9, 110.7, 66.4, 35.5, and 32.3. *Anal.* Calcd for $C_{21}H_{19}N_3S$: C 73.01, H 5.54, N 12.16; Found: C 72.78, H 5.60, N 12.55.

Cyclization of the Intermediate Products. General Procedure:

Zinc chloride (1.36 g, 10 mmol) was added to a solution of an appropriate alkylated product (5 mmol) in dry CH_2Cl_2 (20 ml) and the mixture refluxed for 12 h, cooled to room temperature, and poured into H_2O (20 ml). The aqueous phase was washed with CH_2Cl_2 (3 × 10 ml), and the combined organic layers washed with aqueous NaOH (1 N, 2 × 10 ml), water (2 × 10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by column chromatography (silica gel, hexane). Phenanthrene and naphthalene were compared to the respective authentic samples.

1-Phenylthio-1,2,3,4-tetrahydronaphthalene (4a): Colorless oil. ^{1}H-Nmr δ: 7.48-7.36 (m, 3H), 7.34-7.20 (m, 3H), 7.18-7.03 (m, 3H), 4.55 (t, 1H, J=3.9 Hz), 2.87-2.66 (m, 2H), 2.29-2.14 (m, 1H), 2.08-1.88 (m, 2H), and 1.80-1.69 (m, 1H). ^{13}C-Nmr δ: 137.5, 136.1, 135.4, 131.8, 130.5, 129.2, 128.9, 127.0, 126.9, 125.6, 47.6, 29.1, 28.4, and 18.6. HRms, *m/z* 240.0969 ($C_{16}H_{16}S$ requires 240.0970).

4-Phenylthiochroman (4b): Colorless oil. ^{1}H-Nmr δ: 7.51-7.43 (m, 2H), 7.41-7.25 (m, 4H), 7.18-7.10 (m, 1H), 6.91-6.80 (m, 2H), 4.56-4.46 (m, 2H), 4.27-4.18 (m, 1H), 2.29-2.17 (m, 1H), and 2.05-1.96 (m, 1H). ^{13}C-Nmr δ: 155.0, 134.8, 132.0, 130.9, 129.1, 128.9, 127.4, 120.7, 120.2, 117.0, 62.1, 42.8, and 27.6. HRms, *m/z* 242.0769 ($C_{15}H_{14}OS$ requires 242.0765).

1-Phenylthio-2,3-dihydrophenalene (4c): Light-yellow oil. ^{1}H-Nmr δ: 7.76-7.64 (m, 2H), 7.49-7.18 (m, 9H), 4.81 (t, 1H, J=3.6 Hz), 3.68-3.53 (m, 1H), 2.98-2.90 (m, 1H), and 2.30-2.11 (m, 2H). ^{13}C-Nmr δ: 135.0, 134.6, 133.8, 133.7, 132.8, 129.0, 128.9, 127.7, 127.3, 126.0, 125.6, 125.5, 125.1, 124.4, 49.0, 27.2, and 26.1. *Anal.* Calcd for $C_{19}H_{16}S$: C 82.57, H 5.83; Found: C 82.72, H 5.92.

1-Phenylthioindan (4f): Colorless oil. ^{1}H-Nmr δ: 7.31-7.15 (m, 7H), 7.13-7.09 (m, 2H), 4.35 (t, 1H, J=6.8 Hz), 2.91 (t, 2H, J=7.3 Hz), and 2.19-2.10 (m, 2H). ^{13}C-Nmr δ: 140.6, 134.0, 132.5, 128.8, 128.5, 128.4, 127.6, 126.1, 56.8, 37.0, 32.9. HRms, *m/z* 227.0890 ($C_{15}H_{14}S$ requires 227.0894).

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