Facile Preparation of Benzo[4,5]thieno[2,3-*b*]pyridines and Naphtho[*b*-4,5]thieno[2,3-*b*]pyridines via the Reaction of Barton Esters and Benzynes

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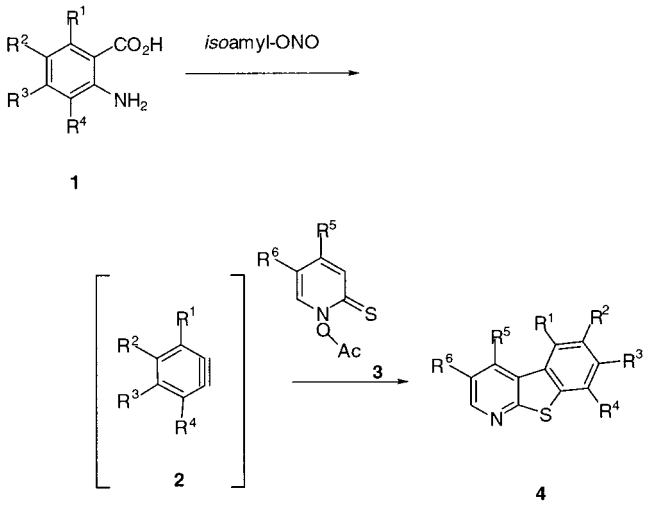
Titled compounds were prepared in a one-pot synthesis by generating symmetrically substituted benzyne intermediates by the diazotization of anthranilic acids in the presence of Barton esters. Unsymmetrically substituted aryne either gave mixtures of regioisomers or failed. However, nitro and methyl derivatives of titled compounds could be obtained as single products using appropriately substituted Barton esters.

The chemistry of 1,2-arynes is accepted today as an important addition to synthetic design.[1] These intermediates have been used as versatile precursors in a number of synthetic reactions. The arynes are powerful electrophilic intermediates, whose substituted derivatives can undergo regioselective additions[2] with a variety of nucleophiles.[3] These properties have been used in the synthesis of a number of heterocycles and polynuclear hydrocarbons with substitution patterns not easily obtained from standard aromatic substitution methods.[4] Additionally, the dienophilic nature of the arynes have been exploited in [2 + 2] and [4 + 2] cycloaddition reactions with enes and dienes.[5]

Although the nature of the singlet and triplet electronic states of *ortho*-, *meta*-, and *para*-benzynes[6] and their reactivity in the gas phase[7] have been investigated, very little has been reported on the involvement of free radicals in aryne reactions in solution. Two of these studies indicated that aryne reacted with tertiary amines[8] and diaryl sulfides[9] to give nitrogen and sulfur ylides, respectively, by the usual nucleophilic addition pathway. However, chemical-induced dynamic nuclear polarization was observed in these intermediates (using ^{1}H NMR techniques), which indicated these initially formed aryne adducts underwent a free-radical dissociation-recombination rearrangement via a radical-pair intermediate to the observed products. Other studies have suggested that benzyne reacts with highly strained polycyclics[10] and vinylcyclopropanes[11] via diradical intermediates.

Scheme 1



Recently, benzyne was found to undergo 1,4 addition reactions with 2-pyridylcarboxylate-pyridones to give 1-(2-acylphenyl)-2-pyridones.[5] These novel results suggested that a study of reaction of the corresponding sulfur derivatives, such as the *O*-acyl derivatives of thiohydroxamic esters (Barton esters)[12] with arynes under similar conditions might be worthy of study. Since Barton esters are known to be photolabile precursor of carbon radicals, it was of interest to see if radicals may be involved in these reactions.

Anthranilic acid aryne precursors (**1a**−**f**) and Barton esters (**3a**−**d**) chosen for study are shown in Figure 1. The reactions were run under subdued lighting in order to moderate the decomposition of **3a**−**d**. As shown in Scheme 1, benzyne (**2a**), generated from anthranilic acid (**1a**), and 3,4,5,6-tetraphenylbenzyne (**2b**), generated

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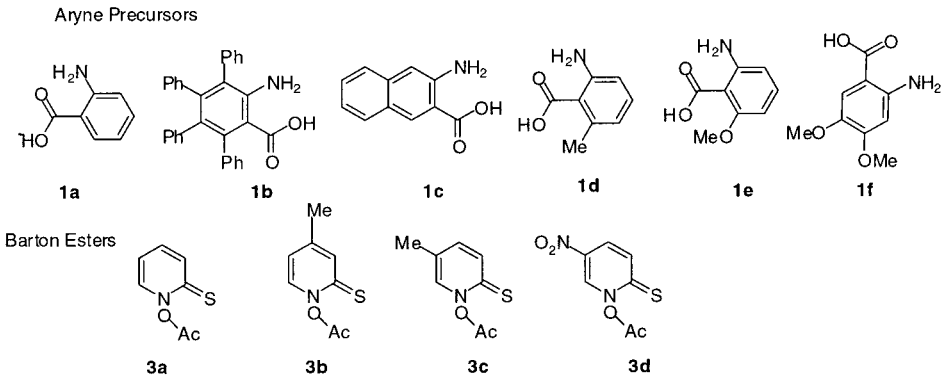

Figure 1.

Table 1. Yields of Compounds 4a−l

	R^1	R^2	R^3	R^4	R^5	R^6	yield,%
a	H	H	H	H	H	H	52
b	H	H	H	H	Me	H	55
c	H	H	H	H	H	Me	52
d	H	H	H	H	H	NO_2	56
e	Ph	Ph	Ph	Ph	H	H	23
f	Ph	Ph	Ph	Ph	Me	H	27
g	Ph	Ph	Ph	Ph	H	Me	21
h	Ph	Ph	Ph	Ph	**4**	NO_2	18
i	H	CH=CH	CH=CH	H	H	H	49
j	H	CH=CH	CH=CH	H	Me	H	48
k	H	CH=CH	CH=CH	H	H	Me	51
l	H	CH=CH	CH=CH	H	H	NO_2	51

from 3,4,5,6-tetraphenyl derivative **1b**, were found to react with Barton esters (**3a**−**d**) to give benzo- (**4a**−**d**) and 5,6,7,8,-tetraphenybenzol[4,5]thieno[2,3-*b*]pyridines (**4e**−**h**), respectively.

The low yields (shown in Table 1) of **4e**−**h** (21−32%) probably reflect steric effects and the low solubility of **1b** in methylene chloride solvent. In addition, 2,3-naphthalyne (**2c**), generated from 3-amino 2-naphtholic acid (**1c**), was found to react with esters **3a**−**d** to provide naphtho[*b*-4,5]thieno[2,3-*b*]pyridines (**4i**−**l**) in modest yields. The unsymmetrical 3-methylbenzyne (**2d**), generated from 3-methylanthranilic acid (**1d**), reacted with the unsubstituted Barton ester **3a** nonregioselectively to yield a 1:1 mixture of 5- and 8-methylbenzo[4,5]thieno[2,3-*b*]-pyridine that resisted separation by usual chromatographic techniques. Similar treatment of 3-methoxy- (**1e**) and 4,5-dimethoxyantranilic acids (**1f**) with ester **3a** gave complex mixture of unidentifiable compounds. The importance of steric effects in these reactions was further demonstrated by the fact that replacement of the *N*-acetate group with *N*-pivaloate in the Barton ester resulted in depressed yields (∼20%).

The structures of **4b**−**l** were ascertained by ^{1}H and ^{13}C NMR spectroscopy, as well as MS and elemental analyses. The structures of **4i** and **4f** were further confirmed by single-crystal X-ray crystallography. The X-ray data reveal that the 4-methyl group in the tetraphenyl derivative **4f** is located across from the cavity of the 5-phenyl ring, which is perpendicular to the benzo ring. Consequently, the proton chemical shift of the 4-methyl group in **4f** occurs at a chemical shift (δ = 1.51 ppm) lower than that (δ = 2.98 ppm) of the 4-methyl group in **4b**. Similar differences in chemical shifts of the 4-H in in the 3-methyl derivatives **4g** (δ = 6.49 ppm) and **4c** (δ = 8.18 ppm) are also observed.

There is insufficient data upon which to propose a mechanism for this reaction. However, on the basis of the known nucleophilicity of sulfur, it is possible that Barton esters would react with benzyne, perhaps by SET. to give a radical intermediate. CIDNIP results from a previous sulfur/aryne study[9] are consistent with such an intermediate. Barton esters are used to provide a radical source by the regeneration of the pyridine ring in the special version of the Julia synthesis.[13] We are carrying out studies on elucidating the mechanism of this reaction.

Irrespective of the mechanism, this arynic reaction provides a convenient method for preparing sulfur- and nitrogen-containing tricylic and tetracyclic heterocycles, which competes well with the two most commonly used multistep syntheses.[14,15] Although compounds such as **4** are rare, they have been found to be annulated NADH models with very good activity under mild laboratory conditions.[16] Furthermore, they are of pharmaceutical interest due to their isosterism with indolopyridines.[17]

Experimental Section

General Data. Melting points are uncorrected with respect to stem correction. IR spectra were recorded on a FTIR spectrometer, and the ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz multinuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard.. Elemental analyses were obtained from SMU Analytical Services Laboratories. With the exception of 5,6,7,8-tetraphenylanthranilic acid (**1b**), the anthranilic acids (**1a**,**c**, and **d**) were obtained from commercial sources. Compounds **1b**[18] and Barton esters **3a**−**d**[13] were prepared by literature procedures. Barton esters were stored in an ambered bottle in a refrigerator, and glassware was heated at 125 °C in an oven overnight prior to use. All benzyne reactions were done under an atmosphere of dry O_2-free N_2 via balloon.

General Synthesis of Compounds 4a−l. All reactions were carried out under subdued lighting. A solution of anthranilic acid (**1**, 1.0 mmol) dissolved in 5 mL of acetone was added dropwise over 45−60 min to a refluxing mixture containing Barton ester (**3**, 1.0 mmol) and isoamylnitrite (3.0 mmol) in 10 mL of dichloromethane. The resulting solution was refluxed for an additional 3 h. Then, the solution was cooled to room temperature, and the solvent was evaporated to give crude product mixture. The mixture was purified by silica gel chromatography with a mixture of 5% ethyl acetate

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in hexane as eluent to give the desired product (**4**). The physical properties of **4** are given below.

Benzo[4,5]thieno[2,3-*b*]pyridine (4a). Colorless solid, mp 75−76 °C (lit.[15] 73−74 °C).

4-Methylbenzo[4,5]thieno[2,3-*b*]pyridine (4b). Light tan solid, mp 75−77 °C; R_f = 0.21 (hexane/ethyl acetate = 9:1). IR (KBr): 3054, 2955, 1571, 1552, 1440, 738, 572 cm^{-1}. ^{1} H NMR ($CDCl_3$): δ 2.79 (s, 3 H), 7.08 (d, J = 4.8 Hz, 1 H), 7.42−7.45 (m, 2 H), 7.82 (d, J = 9.2 Hz, 1 H), 8.16 (d, 9.2 Hz, 1 H), 8.42 (d, J = 4.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 21.6, 121.0, 122.9, 124.6, 125.2, 126.6, 128.0, 133.8, 137.9, 143.3, 147.4. Anal. Calcd for $C_{12}H_{29}NS$ (199.05): C, 72.33; H, 4.55; N, 7.03. Found: C, 72.31; H, 4.63; N, 7.10. MS(EI): m/z 199 (M^+, 100), 171 (10), 154 (5).

3-Methylbenzo[4,5]thieno[2,3-*b*]pyridine (4c). Viscous liquid; R_f = 0.18 (hexane/ethyl acetate = 19:1). ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3 H), 7.48−7.51 (m, 2 H), 7.87 (d, J = 7.19, 1 H), 8.10 (d, J = 6.8 Hz, 1 H), 8.18 (s, 1 H), 8.49 (s, 1 H). ^{13}C NMR ($CDCl_3$): 18.4, 121.9, 123.01, 124.6, 127.3, 129.0, 129.1, 132.6, 138.4, 149.3, 159.0. MS(EI): m/z 199 (M^+, 100), 171-(10), 127 (5). Anal. Calcd for $C_{12}H_9NS$ (199.05): C, 72.33; H, 4.55; N, 7.03. Found: C, 72.38; H, 4.60; N, 7.02.

3-Nitrobenzo[4,5]thieno[2,3-*b*]pyridine (4d). Colorless solid, mp 210−211 °C; R_f = 0.46 (hexane/ethyl acetate = 9:1). IR (KBr): 3068, 1580, 1571, 1512, 1338, 892, 771, 645, 586. ^{1}H NMR ($CDCl_3$):: δ 7.59−7.67 (m, 2 H), 7.95 (d,d J = 6.4 Hz, 1.2 Hz, 1 H), 8.25 (d,d J = 7.2, 2.0 Hz, 1 H), 9.14 (d, J = 2.4 Hz, 1 H), 9.48 (d, J = 2.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$): 121.8, 122.2, 123.1, 124.13, 126.4, 127.2, 129.9, 136.4, 140.1, 141.3, 164.6. Anal. Calcd for $C_{11}H_6N_2O_2S$ (230.24): C, 57.38; H, 2.62: N, 12.17. Found: C, 57.45; H, 2.66; N, 12.22.

5,6,7,8-Tetraphenylbenzo[4,5]thieno[2,3-*b*]pyridine (4e). Colorless solid, mp 330−332 °C; R_f = 0.36 (hexane/ethyl acetate = 9:1). IR (KBr): 3056. 1600, 1552, 1497, 1384, 698, 569, 417 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.76 (dd, J = 8.3, 1.5 Hz, 1 H), 6.86−6.91 (m, 10 H), 6.95−6.98 (dd, J = 4.6, 1.5.Hz, 1 H), 7.24−7.36 (m, 10 H), 8.49 (dd, J = 4.60, 1.51. 1 H). ^{13}C NMR (DMSO-d_6): δ 119.80, 126.26, 126.44, 127.22, 127.37, 128.09, 128.83, 129.19, 130.27, 130.26, 130.41, 130.49, 131.62, 131.78, 132.32, 135.80, 138.35, 138.77, 139.69, 139.74, 139.86, 140.14, 140.19, 148.29, 162.49. Anal. Calcd for $C_{35}H_{23}NS$ (489.16): C, 85.86; H, 4.73; N, 2.86. Found: C, 85.93; H, 4.78; N, 2.93.

4-Methyl-5,6,7,8-tetraphenylbenzo[4,5]thieno[2,3-*b*]pyridine (4f). Colorless solid, mp 290−292 °C; R_f = hexane/ethyl acetate = 9:1). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 3 H), 6.73−6.85 (m, 2 H), 6.83−6.85 (m, 2 H), 6.87−6.92 (m, 7 H), 7.05−7.07 (m, 2 H), 7.12−7.14 (m, 3 H), 7.25−7.31 (m, 5 H), 8.37 (d, J = 4.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 22.6, 122.3, 125.4, 125.7, 126.6, 126.7, 127.5, 127.7, 128.2, 130.0, 130.2, 131.1, 131.7, 131.8, 135.5, 127.9, 139.4, 139.7, 139.8, 140.1, 131.9, 145.2, 147.1, 163.0. Anal. Calcd for $C_{36}H_{25}NS$ (503.17): C, 85.85; H, 5.00; N, 2.78. Found: C, 85.90; H, 4.98; N, 2.83.

3-Methyl-5,6,7,8-tetraphenylbenzo[4,5]thieno[2,3-*b*]pyridine (4g). Colorless solid, mp 252−254 °C; R_f = hexane/ethyl acetate = 19:1). ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3 H), 6.49 (d, J = 1.4 Hz, 1 H), 6.89−6.90 (m, 10 H), 7.23−7.35 (m, 10 H), 8.34 (d, J = 1.6 Hz, 1 H). ^{13} C NMR ($CDCl_3$): δ 18.6, 125.6, 125.8, 126.7, 127.3, 127.4, 128.2, 128.5, 130.0, 130.2, 130.3, 131.4, 132.8, 135.6, 137.8, 139.0, 139.5, 139.6, 139.6, 139.8, 148.6, 159.9. Anal. Calcd for $C_{36}H_{25}NS$ (503.17): C, 85.85; H, 5.00; N, 2.78. Found: C, 85.78; H, 4.96; N, 2.85.

3-Nitro-5,6,7,8-tetraphenylbenzo[4,5]thieno[2,3-*b*]pyridine (4h). Colorless solid, mp 260−263 °C; R_f = 0.35 (hexane/ethyl acetate = 9:1). ^{1}H NMR (DMSO-d_6): δ 6.70−7.35 (m, 17 H), 7.48 (d, J = 8.80 Hz, 1 H), 7.58 (d, J = 8.80 Hz, 1 H), 7.75 (d, J = 8.80 Hz, 1 H), 8.16 (dd, J = 9.00, 2.6 Hz, 1 H). 9.20 (d, J = 2.4 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 122.71, 124.61, 125.96, 127.17, 128.18, 128.31, 129.45, 130.12, 131.46, 131.70, 133.78, 135.71, 143.10, 145.00, 168.22. Anal. Calcd for $C_{35}H_{22}N_2O_2S$: C, 78.63; H, 4.15; N, 5.24. Found: C, 78.70; H, 4.2-; N, 5.30.

Naphtho[*b*-4,5]thieno[2,3-*b*]pyridine (4i). Colorless solid, mp 190−191 °C; R_f = 0.26 (hexane/ethyl acetate = 9:1). ^{1}H NMR ($CDCl_3$): δ 7.39 (d,d, J = 7.8, 4.7 Hz, 1 H), 7.54 (m, 2 H), 7.93 (d, J = 7.1 Hz, 1 H), 8.01 (d, J = 7.6 Hz, 1 H), 8.28 (s, 1 H), 8.42 (dd, J = 7.9, 1.7 Hz, 1 H), 8.56 (s, 1 H), 8.64 (dd, J = 4.7, 1.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 199.53, 120.88, 121.07, 125.49, 126.48, 127.13, 128.32, 128.95, 129.29, 130.86, 132.56, 132.85, 135.75, 148.95, 162.89. MS(EI) m/z 235 (M^+ 100), 117 (5), 104 (4). Anal. Calcd for $C_{15}H_9NS$ (235.305): C, 76.56; H, 3.86; N, 5.95. Found: C, 76.60; H, 3.98; N, 5.88.

4-Methylnaphtho[*b*-4,5]thieno[2,3-*b*]pyridine (4j). Colorless solid, mp 163−165 °C; R_f = 0.58 (hexane/ethyl acetate = 4:1). IR (KBr): 3052, 2921, 1595, 1551, 1425, 1370. 1199. 875, 740, 474 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.98 (s, 3 H), 7.16 (d, J = 4.9 Hz, 1 H), 7.50−7.55 (m, 2 H), 7.90 (d, J = 7.84 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.29 (s, 1 H), 8.47 (d, J = 4.8 Hz, 1 H), 8.69 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 21.9, 120.9, 122.3, 124.7. 125.3, 126.6, 126.8, 128.7. 130.9, 132.0, 133.5, 135.8. 143.7, 148.0, 162.9. MS m/z 249 (M^+, 100), 221 (10), 124 (15). Anal. Calcd for $C_{16}H_{11}NS$ (249.33): C, 77.07; H, 4.45; N, 5.62. Found: C, 77.10; H, 4.44; N, 5.62.

3-Methylnaphtho[*b*-4,5]thieno[2,3-*b*]pyridine (4k). Colorless solid, mp 145−147 °C; R_f = 0.36 (hexane/ethyl acetate = 19:1). ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3 H), 7.50−7.57 (m, 2 H), 7.91 (d, J = 5.3 Hz, 1 H), 8.0 (d, J = 7.4 Hz, 1 H), 8.21 (d, J = 1.0 Hz, 1 H), 8.25 (s, 1 H), 8.48 (d, J = 1.1 Hz, 1 H), 8.52 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 18.5, 120.8, 121.1, 125.5, 126.5, 127.2, 128.4, 129.2, 129.3, 129.7, 130.9, 132.6, 132.9, 136.3, 149.5, 159.7. MS(EI) m/z 249 (M^+, 100), 221 (5), 124 (7), 110 (5). Anal. Calcd for $C_{16}H_{11}NS$ (249.33): C, 77.07; H, 4.45; N, 5.62. Found: C, 77.02; H, 4.40; N, 5.69.

3-Nitronaphtho[*b*-4,5]thieno[2,3-*b*]pyridine (4l). R_f = 0.35 (hexane/ethyl acetate 9:1). ^{1}H NMR ($CDCl_3$): δ 7.50−7.70 (m, 2 H), 7.96 (d, J = 6.7 Hz, 1 H), 8.10 (d, J = 7.6 Hz, 1 H), 8.35 (s, 1 H), 8.71 (s, 1 H), 9.18 (d, J = 1.6 Hz, 1 H), 9.45 (d, J = 1.12 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 122.71, 124.61, 125.96, 127.17, 128.18, 128.31, 129.45, 130.12, 131.46, 131.70, 133.78, 135.71, 143.10, 145.00, 168.22. Anal. Calcd for $C_{15}H_8N_2O_2S$ (280.30): C, 62.47; H, 2.88; N, 9.99. Found: C, 62.59; H, 2.93; N, 10.07.

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Supporting Information Available: X-ray diffraction data for compounds **4f** and **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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