A one-step synthesis of 1-substituted thieno[2,3-*f*]benzo[*cd*]indol-4-ones *via* benzyne-3-carboxylate

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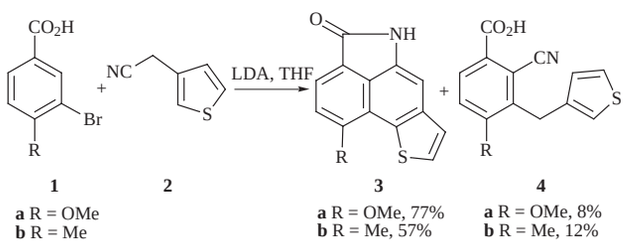
1 PERKIN COMMUNICATION

4-Substituted bromobenzoic acids react with 3-thienylacetonitrile under aryne-forming conditions (LDA) to give the corresponding thieno[2,3-*f*]benzo[*cd*]indol-4-ones; this constitutes the first reported synthesis of this heretofore unknown tetracyclic heterocycle.

During the course of our investigation of the effect of negatively charged substituents on the chemistry of benzynes, we found that 4-methoxy-3-bromo- (**1a**) and 4-methyl-3-bromobenzoic acids (**1b**) react with 3-thienylacetonitrile **2** to yield the corresponding 1-methoxy- (**3a**) and 1-methyl-thieno[2,3-*f*]-benzo[*cd*]indol-4(5*H*)-ones (**3b**) in yields of 77 and 57%, respectively (Scheme 1). In addition, a small amount of



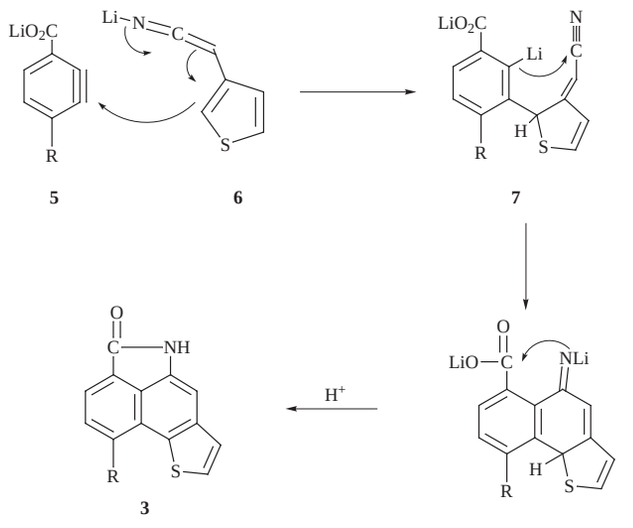
Scheme 1

2-cyano-4-methoxy-3-(3-thienylmethyl)benzoic acid (**4a**, 8%) and 2-cyano-4-methyl-3-(3-thienylmethyl)benzoic acid (**4b**, 12%) were obtained from the reactions of acids **1a** and **1b**, respectively.

These one-step reactions were carried out at −70 °C using a reverse-addition procedure[1] in which a solution of acid **1** (5 mmol) in THF was added to a solution containing LDA (15 mmol) in THF at −70 °C. After addition of compound **2** and stirring for 30 min, the resulting solution was then warmed to room temperature, quenched, and worked up in the usual way to give products **3** and **4**. The structures of these products were assigned on the basis of ^{1}H NMR, ^{13}C NMR and HRMS analyses.

The minor products **4a** and **4b** most likely are formed *via* a tandem addition–rearrangement aryne pathway.[2] Interestingly, acids **1a** and **1b** react with phenylacetonitrile and several of its methoxy derivatives as well as 2-thienylacetonitrile under similar conditions to afford rearranged 3-arylmethyl-2-cyanobenzoic acids,[3] however, no indol-2-one products were detected in these reactions.

Compounds **3a** and **3b** are probably formed by a novel step-wise [2 + 4] cycloaddition outlined in Scheme 2. As shown, the appropriate benzyne-3-carboxylate **5** adds to the 2-position of the thiophene ring and the nitrile carbon atom of the α-lithiated 3-thienylacetonitrile **6** to give adduct **7**. Adduct **7** then collapses to the tricyclic intermediate **8**, which undergoes further cyclization and aromatization to the product **3**. The orientation of addition to **5** is consistent with that observed in nucleophilic addition of arylacetonitrile anions to benzyne-3-carboxylate.[4] Base-initiated step-wise intermolecular [2 + 4]



Scheme 2

cycloaddition reactions have been observed with benzynes and dipolar nucleophiles such as 3-lithiated-3-cyanophthalides[5] and α-cyano-*o*-tolunitrile.[6] However, to our knowledge, this is the first reported example of a lithiated anion of a heteroarylacetonitrile participating in such a process.

In conclusion, the one-step, low temperature reactions reported herein results in the concomitant construction of a fused thiophene onto a benzo[*cd*]indol-2(1*H*)-one from readily available starting materials. This constitutes a synthesis of an heretofore unknown thieno[2,3-*f*]benzo[*cd*]indol-4(5*H*)-one ring system. This synthesis may also prove valuable for preparing intermediates in drug synthesis. For example, several natural and unnatural products, which contain the benzo[*cd*]-indol-2(1*H*)-one basic skeleton, *e.g.* ergot[6] and Aristolactam[7,8] alkaloids, have been found to have potentially significant biological active properties. Many of these serve as inhibitors of thymidylate synthase,[9] cardiovascular agents,[10] selective serotonin uptake inhibitors[11] and antihypertensive agents.[12]

Experimental

General data

Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR™ 550 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 multinuclear NMR spectrometer; chemical shifts were referenced to $SiMe_4$ as internal standard and coupling constants *J* are given in Hz. High resolution mass spectra were performed by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant Np. P41RR0954). 3-Bromo-4-methoxybenzoic acid **1a**, 3-bromo-4-methylbenzoic acid **1b** and thienylacetonitrile **2** were purchased from Aldrich Chemical

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Company. Diisopropylamine was refluxed over and distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from Na–benzophenone immediately prior to use. *n*-Butyllithium (Bu^{n}Li) was purchased from Aldrich Chemical Company as a solution in hexane. The glassware was heated at 125 °C in an oven overnight prior to use. All reactions were done under an atmosphere of dry O_2-free N_2 *via* balloon.

General procedure for arynic reactions

In a flame-dried flask flushed with nitrogen, fresh LDA (15 mmol) was prepared by adding Bu^{n}Li (15 mmol, 2.5 M in hexane) to a solution of diisopropylamine (15 mmol) in THF (30 ml) at −70 °C. After stirring for 10 min, the appropriate aryne precursor **1** (5 mmol) in THF (30 ml) was added dropwise over 20 min, and the stirring was continued for 10 min at −70 °C. A solution of the thienylacetonitrile **2** (185 mg, 15 mmol) was then added during which the solution developed a deep red color. The resulting solution was stirred for an additional 30 min, allowed to warm to room temperature, stirred overnight, and quenched with sat. aq. NH_4Cl (30 ml) to give a crude mixture, which ^{1}H NMR showed to contain the indolone **3** and the rearranged nitrile **4**. The indolones could be obtained in pure form by washing first with water then with methylene chloride. Evaporation of the methylene chloride extracts followed by flash column chromatography (silica gel) using a mixture of hexane–acetone (6:4) gave the rearranged nitrile. Percentage yields and pertinent physical and spectral data of **3** and **4** are shown below.

1-Methoxythieno[2,3-*f*]benzo[*cd*]indol-4(5*H*)-one 3a. 77%, light brown solid, mp 300 °C (decomp.); δ_H(400 MHz; [$^2H_6$]DMSO) 4.02 (s, 3 H), 7.11 (d, *J* 7.6, 1 H), 7.54 (d, *J* 5.6, 1 H), 7.74 (d, *J* 5.6, 1 H), 7.94 (d, *J* 7.6, 1 H), 8.09 (s, 1 H), 11.09 (s, 1 H); δ_C(400 MHz; [$^2H_6$]DMSO) 56.3, 106.2, 109.0, 118.1, 118.3, 118.6, 122.2, 125.0, 125.8, 128.9, 131.5, 142.4, 160.0, 168.2 ($C_{14}H_9NO_2S$ requires M^+, 255.2906. Found: *M*, 255.2902).

1-Methylthieno[2,3-*f*]benzo[*cd*]indol-4(5*H*)-one 3b. 57%, light brown solid, 280 °C; δ_H(400 MHz; [$^2H_6$]DMSO) 2.81 (s, 3 H), 7.60 (d, *J* 7.2, 1 H), 7.62 (d, *J* 5.6, 1 H), 7.84 (d, *J* 5.6, 1 H), 7.94 (d, *J* 7.2, 1 H), 8.21 (s, 1 H), 11.20 (s, 1 H); δ_C(400 MHz; [$^2H_6$]DMSO) 18.3, 111.4, 117.9, 121.0, 123.5, 124.2, 124.9, 126.3, 127.7, 129.3, 132.3, 140.8, 143.0, 168.7 ($C_{14}H_9NOS$ requires M^+, 239.2912. Found: *M*, 239.2916).

2-Cyano-4-methoxy-3-(3-thienylmethyl)benzoic acid 4a. 8%, colorless solid; ν_{max}/cm^{-1} 2250 (aromatic CN); δ_H(400 MHz; [$^2H_6$]acetone) 3.89 (s, 3 H), 4.09 (s, 2 H), 7.02 (d, *J* 7.6, 1 H), 7.30 (d, *J* 7.6, 1 H), 7.71 (d, *J* 7.6, 1 H), 8.15 (s, 1 H) ($C_{14}H_{11}NO_3S$ requires M^+, 273.0459. Found: *M*, 273.0457).

2-Cyano-4-methyl-3-(3-thienylmethyl)benzoic acid 4b. 12%, colorless solid; ν_{max}/cm^{-1} 2253 (aromatic CN); δ_H(400 MHz; [$^2H_6$]acetone) 2.34 (s, 3 H), 4.23 (s, 3 H), 7.19 (d, *J* 8.0, 1 H), 7.39 (d, *J* 7.8, 1 H), 7.95 (d, *J* 8.0, 1 H), 7.97 (d, *J* 7.8, 1 H), 8.26 (s, 1 H) ($C_{14}H_{11}NO_2S$ requires M^+, 257.3064. Found: *M*, 257.3062).

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