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A New Concise Strategy for Synthesis of Dibenzo[*b,f*]thiepins and Related Fused Symmetrical Thiepin Derivatives

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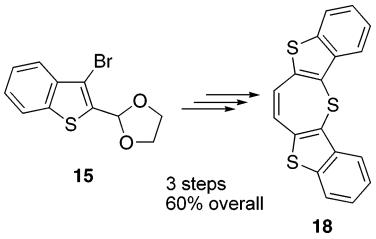

A new strategy for preparation of dibenzo[*b,f*]thiepins and related fused systems in good overall yields is described, featuring ortho-metalation of aromatic or heterocyclic aldehyde acetals followed by treatment with bis(phenylsulfonyl) sulfide for construction of the required bis(aryl)- or bis(heteroaryl) sulfide precursors, which were thereafter subjected to deacetalization, and finally McMurry coupling as the ring-forming step.

The thiepins,[1] including the condensed ring system dibenzo[*b,f*]thiepin (**1**),[1c] have attracted considerable attention over the years, for instance, in connection with theoretical studies concerning aromaticity. More importantly, it has also been demonstrated that several dibenzo[*b,f*]thiepin derivatives display potent biological activities, as illustrated, for example, by the molecule zotepine (**2**), which has psychosedative and antipsychotic properties,[2] or the prostaglandin antagonist **3** (Figure 1).[3] A series of compounds based on this ring system has also been evaluated for antiestrogenic affects.[4] The interest for dibenzo[*b,f*]thiepins in pharmacological applications has exerted considerable impact on the development of their chemistry, resulting in hundreds of papers and patents.[1c] However, despite the numerous publications on the subject, there are only a few synthetic routes to dibenzo[*b,f*]thiepin derivatives available, namely acid-induced rearrangement of 9-(hydroxymethyl)-thioxanthene *p*-toluenesulfonate,[5] Friedel−Crafts-type cyclization of 2-(2-arythiophenyl)acetic acids, followed by further elaboration of the resulting 10,11-dihydrodibenzo[*b,f*]thiepin-10-one derivatives,[6] or treatment of bis(aryl) sulfides with chloroacetyl chloride in the presence of $AlCl_3$.[7]

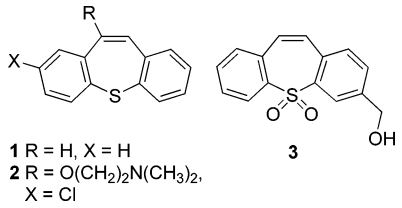

FIGURE 1. Structures of the parent dibenzo[*b,f*]thiepin (**1**) and some biologically active derivatives (**2** and **3**).

Since the existing routes to dibenzo[*b,f*]thiepins either require preparation of elaborate starting materials, or proceed in low overall yields, we embarked upon development of an alternative concise approach starting from readily available 2-bromobenzaldehyde acetals. It is well-established that treatment of metalated aromatics or heteroaromatics with bis(phenylsulfonyl) sulfide[8] provides good yields of bis(aryl) sulfides[9] or bis(heteroaryl) sulfides,[8,10] respectively. Hence, it was envisaged that utilization of lithiated benzenes incorporating masked reactive functional groups ortho to the metal[11] in a similar fashion may give bis(aryl) sulfide intermediates suitable for synthesis of new fused thiepin derivatives. Accordingly, the benzaldehyde acetals **4**[12] and **5**[13] were subjected to halogen−lithium exchange, followed by treatment of the resulting organolithium species with bis(phenylsulfonyl) sulfide to afford the desired bis(aryl) sulfides **6** and **7** (Scheme 1). These compounds were thereafter subjected to acid induced deacetalization providing the known dialdehyde **8**[14] and its derivative **9**, which served as substrates in intramolecular McMurry coupling[15] reactions, eventually giving the known parent dibenzo[*b,f*]thiepin (**1**),[5] as well as the electron-rich substituted system **10**.

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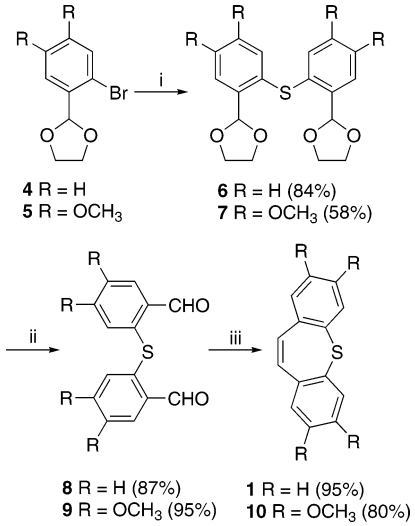
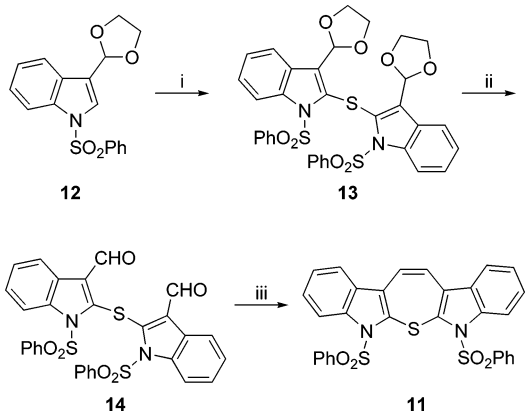
SCHEME 1[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 0.5 h; then $(PhSO_2)_2S$, −78 °C to rt, 16 h; (ii) aq $HClO_4$, acetone, rt, 1−2 h; (iii) $TiCl_4$, Zn, pyridine, THF, reflux, 2.5 h; then **8**/**9**, rt, 16 h; reflux, 4 h; then K_2CO_3, rt, 18 h.

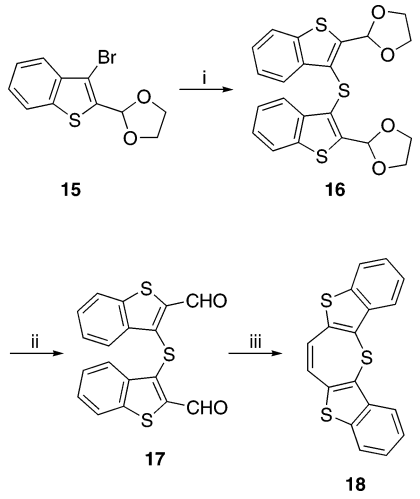
SCHEME 2[a]



[a] Reagents and conditions: (i) LDA, THF, −78 °C, 0.5 h; then $(PhSO_2)_2S$, −78 °C to rt, 16 h, 78%; (ii) aq $HClO_4$, H_2O, 1,4-dioxane, rt, 8 h, 98%; (iii) $TiCl_4$, Zn, pyridine, THF, reflux 2.5 h; then **14**, rt, 16 h; reflux 4 h; then K_2CO_3, rt, 18 h, 79%.

The successful preparation of the dibenzo[*b*,*f*]thiepins **1** and **10** encouraged us to implement this new strategy in a route to the diindolothiepin **11** (Scheme 2). Metalation of the protected indole-3-carboxaldehyde **12**,[16] and subsequent treatment of the resulting lithioindole with bis(phenylsulfonyl) sulfide gave the bis(indolyl) sulfide **13**. Treatment of this material with aqueous perchloric acid in 1,4-dioxane furnished the dicarboxaldehyde **14**, which was finally annulated under McMurry conditions providing the novel ring system **11**. However, all attempts to remove the phenylsulfonyl groups by exposure to bases failed, leading to degradation. This observation could be attributed to the fact that the two electron rich indole units cannot provide enough stabilization for the central thiepin ring. It should be emphasized in this context that many simple thiepins, as well as several fused derivatives, are unstable molecules which undergo decomposition even at moderate temperatures.[1a]

SCHEME 3[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 0.5 h; then $(PhSO_2)_2S$, −78 °C to rt, 16 h, 74%; (ii) aq $HClO_4$, H_2O, acetone, rt, 24 h, 94%; (iii) $TiCl_4$, Zn, pyridine, THF, reflux, 2.5 h; then 17, rt, 16 h; reflux, 4 h; then K_2CO_3, rt, 18 h, 86%.

Likewise, protection of the easily available 3-bromobenzo[*b*]thiophene-2-carboxaldehyde[17] afforded the known acetal **15**,[17a] which was subjected to metalation and subsequent treatment with bis(phenylsulfonyl) sulfide rendering the diacetal **16** (Scheme 3). This product underwent deacetalization providing the dialdehyde **17**, which could eventually be converted to the fused thiepin **18** by intramolecular McMurry coupling. It should also be noted that some related symmetrical thiepins containing two fused thiophene units have previously been prepared in four steps from 2-bromo-3-iodothiophene or 3-bromo-4-iodothiophene in low overall yields.[18]

In conclusion, a new concise route to fused thiepins has been devised, providing convenient access to the parent dibenzo[*b*,*f*]-thiepin, as well as some novel similar condensed systems which are not easily available using the previously published methods. In addition, the use of relatively mild conditions may allow preparation of new pharmacologically relevant fused thiepins bearing sensitive functional groups. It can also be envisaged that variations of this strategy may find applications in syntheses of other closely related fused 7-membered heterocycles.

Experimental Section

Bis(aryl) Sulfide 6. To a solution of the acetal **4** (1.40 g, 6.1 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol) dropwise at −78 °C. The resulting mixture was

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stirred for 30 min followed by addition of a solution of $(PhSO_2)_2S$ (0.97 g, 3.1 mmol) in THF (30 mL) during 15 min. The mixture was allowed to warm slowly to room temperature over 16 h, followed by addition of satd aq NH_4Cl (40 mL). The mixture was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL) and dried (Na_2SO_4). Evaporation of the solvents in vacuo gave a residue which was subjected to column chromatography [*n*-hexane/EtOAc (3:1)] to give **6** (850 mg, 84%) as a yellowish viscous oil: IR (neat) 2885, 1589, 1568, 1468, 1440, 1380, 1208, 1119, 1082, 1051, 969, 940, 766, 749 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.62−7.56 (m, 2H), 7.38−7.30 (m, 4H), 7.12−7.06 (m, 2H), 6.09 (s, 2H), 4.11−3.94 (m, 8H); ^{13}C NMR (DMSO-d_6) δ 138.0 (s), 134.5 (s), 132.4 (d), 130.1 (d), 127.5 (d), 127.0 (d), 100.5 (d), 65.0 (t). Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49. Found: C, 65.55; H, 5.60.

Dialdehyde 8. A solution of aq $HClO_4$ (70%, 0.25 mL) in H_2O (4 mL) was added to a solution of the diacetal **6** (0.59 g, 1.8 mmol) in acetone (8 mL) at room temperature. The mixture was stirred at room temperature for 2 h and was thereafter treated with satd aq $NaHCO_3$ (20 mL). The resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL) and dried (Na_2SO_4), and the solvents were evaporated in vacuo. The residue was triturated with Et_2O to provide the dialdehyde **8** (380 mg, 87%) as a white solid: mp 97−99 °C (lit.[14] mp 95−97 °C).

Dibenzo[*b,f*]thiepin (1). $TiCl_4$ (2.7 mL, 25 mmol) was added cautiously during 10 min to THF (100 mL) at −78 °C under argon atmosphere, and the resulting solution was stirred for 5 min. This slurry was allowed to warm to room temperature, followed by addition of zinc powder (3.3 g, 50 mmol) and pyridine (0.5 mL). The resulting suspension was heated at reflux for 2.5 h. The dialdehyde **8** (121 mg, 0.50 mmol) was added slowly as a dilute solution in THF (100 mL) over 4 h. After the addition was complete, the reaction mixture was allowed to stir at room temperature for 16 h and was thereafter heated at reflux for an additional period of 4 h. After the mixture was cooled to room temperature, a 50% aqueous solution of K_2CO_3 (50 mL) was added. The resulting mixture was stirred vigorously for 18 h and thereafter passed through a pad of Celite, which was washed with EtOAc (40 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Evaporation of the solvents in vacuo, and purification of the residue by column chromatography [*n*-hexane/EtOAc (3:1)], followed by recrystallization from MeOH gave compound **1** (100 mg, 95%) as colorless crystals: mp 86−88 °C (lit.[5] mp 89−90 °C); IR (neat) 1471, 1425, 1263, 1059, 1032, 799, 783, 768, 751, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53−7.50 (m, 2H), 7.33−7.25 (m, 6H), 7.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.3 (s), 134.9 (s), 134.0 (d), 132.8 (d), 129.5 (d), 129.4 (d), 128.4 (d).

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Supporting Information Available: General information, experimental procedures and spectral data for compounds **7**, **9**, **10**, **13**, **14**, **11**, and **16**−**18** and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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