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Synthesis of Thieno-Fused Heterocycles through Reiterative Iodocyclization

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Abstract: Iodocyclization of ethynyl methyl sulfides gives 3-iodo-2-thiomethyl heterocycles, setting up the synthesis of thieno-fused systems through a subsequent iteration of alkyne coupling and iodocylization. This approach can also be exploited in the synthesis of polyfused thiophenes. In developing this protocol it was necessary to address issues associated with unfavourable electronic bias and redox sensitivity in some substrates. The manner in which these have been addressed should prove useful elsewhere in iodocyclization chemisty.

Keywords: cyclization; iodocyclization; sulfur heterocycles; synthetic methods

Thieno-fused thiophenes, pyrroles, furans and their benzo-fused equivalents are valued for their photonic and electronic properties as well as their biological activity (Figure 1).[1,2] While such thiophene ring structures are rare in nature the natural product thienoindoline has been isolated from *Streptomyces albogriseolus,* exhibiting potent plant-growth regulatory properties and inhibition of nitric oxide synthase.[2d,e]

While iodocyclization has emerged as one of the most effective methods for the synthesis of a significant number of heterocycles, its application to polyfused systems has hardly been explored.[3,4] An important subset of these iodocyclization methods, useful in the construction of 5-membered heterocycles, involves reaction of **1** with iodine (Scheme 1). In these cases, iodocyclization is accompanied by concomitant expulsion of an electrofugal methyl group from the heteroatom X as MeI, giving a 3-iodoheterocycle **2**.[3,5] An attractive possibility for the application of this method to polyfused heterocycles is to employ **2** (R = X′Me) in a further alkyne coupling and iodocyclization to give **3** which, in turn, can be subjected to further iterations of alkyne coupling and iodocyclization. Herein, we describe the successful development of such a strategy for the synthesis of thienofused heterocycles **3** (X′ = S).[6] A particular focus of this study has been overcoming some of the inherent limitations that have emerged in the application of iodocyclization to these targets (see below).

Our investigations into a reiterative coupling–iodocyclization strategy centered on ready access to alkynyl methyl sulfides **5** from aryl iodides **4** (Scheme 2). Initial attempts to prepare the benzyl equivalent of **5**, **5′**, by direct coupling of ethynyl benzyl sulfide with **4b** using different Pd-mediated coupling techniques [Sonogashira (M = H), Kumada (M = Mg), Negishi (M = ZnCl) and Stille (M = $SnBu_3$)] were all unsuccessful

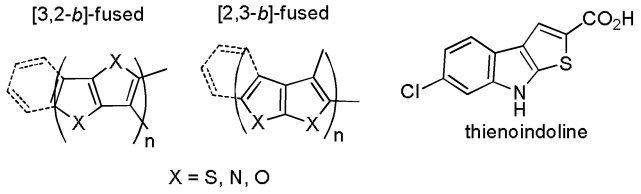
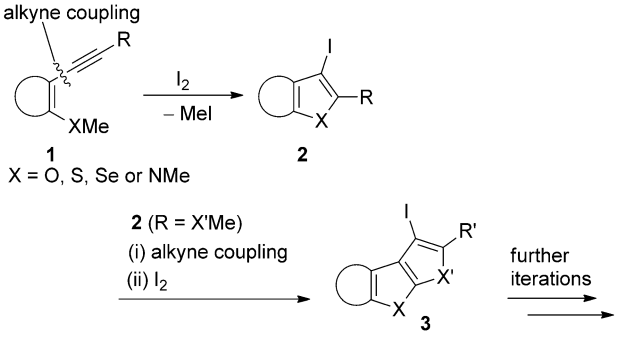
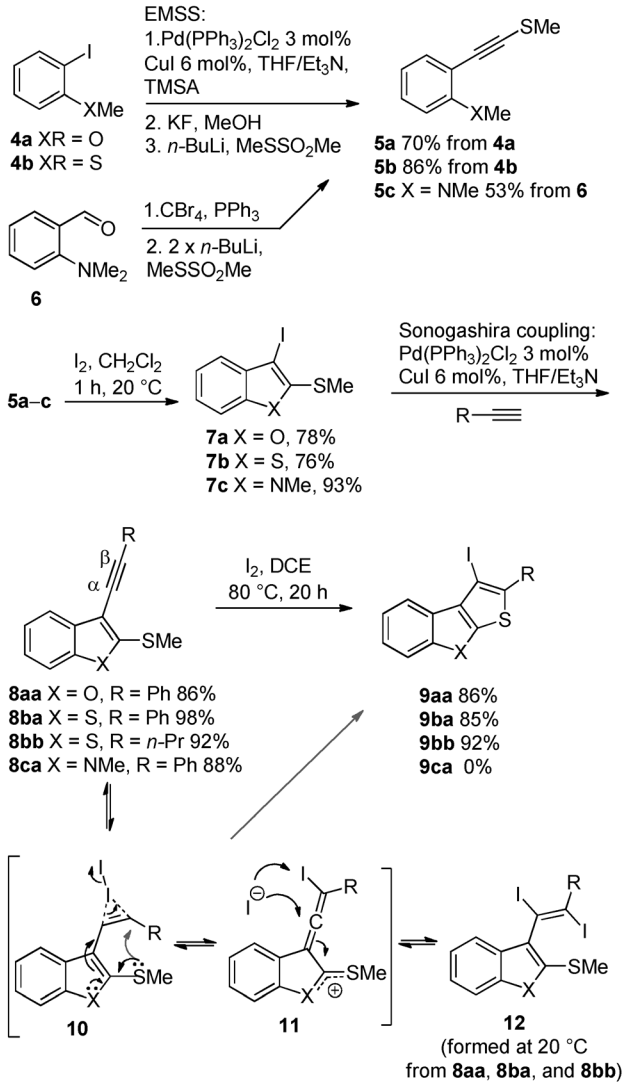


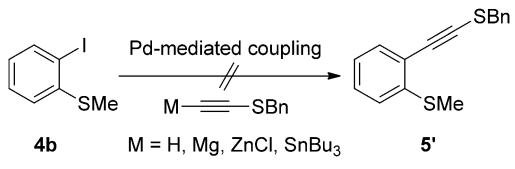
Figure 1. Polyfused 5-membered heterocycles.



Scheme 1. Reiterative approach to fused heterocycles.



Scheme 2. Ethynyl methyl sulfide synthesis (EMSS) and iodocyclization.



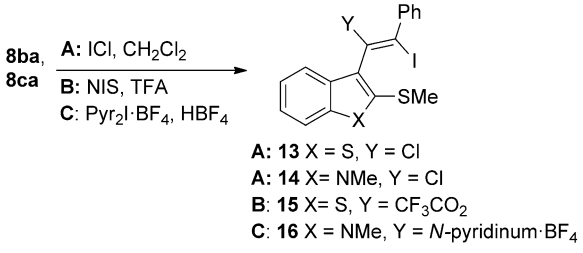
Scheme 3. Attempted formation of **5′** by Pd-coupling.

(Scheme 3), although these efforts are continuing. As an alternative, a three-step ethynyl methyl sulfide synthesis (EMSS) was used for the conversion of **4a, b** to **5a, b** (Scheme 2). This comprised Sonogashira coupling of **4** with trimethylsilylactylene (TMSA), desilylation (KF, MeOH) and methyl sulfide incorporation (*n*-BuLi, $MeSSO_2Me$). This sequence afforded **5a** and **5b** in a good overall yield (70% and 86% from **4a** and **4b**, respectively). While the EMSS is also likely to be successful for the preparation of **5c**, we utilized a sample of the aldehyde **6** we had at hand and converted it to **5c** through a Corey–Fuchs sequence involving *in situ* trapping of the alkynyllithium with $MeSSO_2Me$. In this manner **5c** was achieved in a moderate yield of 51% (from **6**). Iodocyclization of **5a–c** to **7a–c** using iodine in dichloromethane was very efficient (76–93%) and the resultant iodides all underwent efficient Sonogashira coupling to give various 3-alkynyl-2-thiomethyl heterocycles **8aa–ca** in good yield (86–98%).

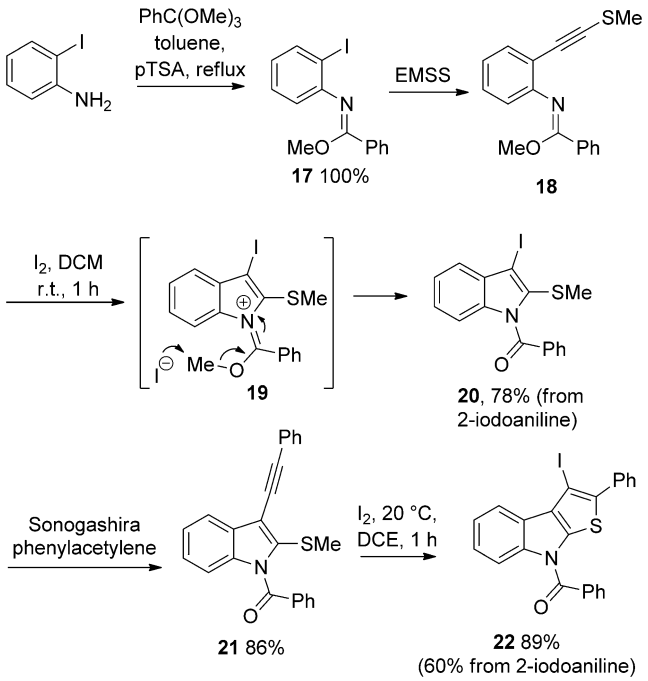
During the course of these studies, Zeni and coworkers[7] also reported on the preparation of and 3-alkynyl-2-thiomethyl heterocycles **8** (X = S and Se), and demonstrated that these could be exploited in electrophile-promoted cyclization using electrophilic selenium and tellurium species. However, the iodocyclization of substrates **8** was not reported. When we initially attempted iodocyclization of **8ba** (iodine in CH_2Cl_2, 20 °C) only 18% conversion to the iodocyclized product **9ba** was achieved, with most of the material being converted to the iodine adduct **12ba**. This preference for **12ba** over the iodocyclized product **9ba** is expected to arise from an unfavourable distribution of electron denisty in the alkyne, where the electron-rich heterocycle (more electron-rich than R) promotes iodine addition by facilitating conversion of **10** to cation **11** that then undergoes attack by the iodide counter ion to give the iodine adduct **12** (black arrows). The rate of conversion of **10** to **11** exceeds the rate of cyclization of **10** to **9** (grey arrows), favouring formation of **12** over **9**.[2b,4l]

Expecting that a reduction in the nucleophilicity of the counter ion in **11** might disfavour addition over iodocyclization we investigated the use of alternative iodonium and bromonium sources such as ICl, NIS, NBS and Barluenga's reagent $[(Pyr)_2I{\cdot}BF_4 + HBF_4]$ on **8ba** and **8ca** (Scheme 4). This was in part successful with NIS giving a modest yield of **8ba** 32% (details not shown). However, all other reagents led to either decomposition or alternative addition products, for example, **13**–**16** (Scheme 4).[8,9]

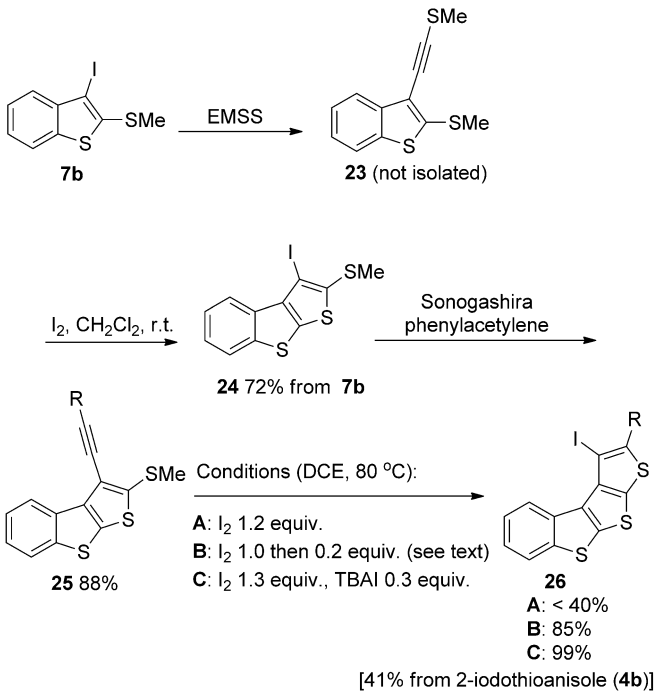
We next investigated if heating the reaction mixtures might promote the reversibility of the process **8**→**12**, providing a steady state concentration of **10**,



Scheme 4. Attempted iododcyclization of **8ba** and **8ca** with different iodonium reagents.



Scheme 5. Revised thieno-fused indole synthesis.



Scheme 6. Poly-[2,3-*b*]-fused thiophene synthesis.

which would undergo irreversible formation of **9** (Scheme 2, grey arrows).[10] Thus, refluxing a solution of **8ba** and iodine (1.2 equivalents) in 1,2-dichloroethane (DCE) enabled conversion of the initially formed iodine adduct **12ba** to the iodocyclized product **9ba** in good yield (85%). A similar outcome was achieved for **8aa** and **8bb**, giving **9aa** (86%) and **9bb** (95%), respectively. However, when the indole equivalent **8ca** was reacted with iodine under the same conditions no iodine adduct was formed and only **8ca** could be detected, which decomposed under the reaction conditions over 24 h at room temperature. Likewise, direct heating of a freshly formed solution **8ca** and iodine in DCE led only to decomposition.

We attributed the inability of **8ca** to cyclize to the high donicity of the group X=NMe, which favours conversion of **10** to **11**, disfavouring iodocyclization and favouring decomposition, possibly through demethylation of the NMe and SMe groups. To address this we decided to counter the degree of stabilization of **11** (X=NMe) by replacing the N-methyl group in **8ca** with an electron-withdrawing benzoyl group. For this purpose we identified a convenient approach to the N-benzoyl equivalent of **8ca**, **20**, starting from 2-iodoaniline (Scheme 5).[11] The methyl benzimidate **17** was formed from condensation of 2-iodoaniline with trimethyl orthobenzoate (100%). This material was converted to the ethynyl methyl sulfide **18** using the previously described EMSS reaction sequence and iodocyclized to **20**. This involved concomitant, conjugative demethylation of the imminium ion **19**, installing the desired benzoyl functionality in **20**. For greater convenience, all of the procedures required to convert 2-iodoaniline to **20** were conducted without intermittent chromatographic purification of synthetic intermediates, giving **20** in 78% overall yield. Sonogashira coupling of **20** to phenylacetylene gave **21** (86%) which, by contrast to other 5-membered fused systems **8**, underwent rapid iodocyclization to **21** at room temperature within 1 h and without any apparent competitive formation of an iodine adduct. The rapid rate of iodocyclization **20**→**21** (89%), contrasts with the unsuccessful reaction **8ca**→**9ca**, and underscores the counter-productive role that the electron-donor groups X play in resisting the iodocyclization of **8** to **9**. The overall conversion of 2-iodoaniline to 3-iodothienoindole **22** was achieved in 60% yield.[12]

We next explored further iterations of the EMSS–iodocyclization protocol towards an extended oligomer **26** (Scheme 6). As with the thieno-fused indole synthesis (above), we undertook the EMSS–iodocyclization sequence of **7b**→**23**→**24** without intermittent chromatographic purification of synthetic intermediates affording **24** in 72% overall yield from **7b**. By contrast with the alkyl- and aryl-substituted alkynes, **8**, ethynyl methyl sulfide **23** underwent direct iodocyclization at room temperature to **24**. In this case, the electronic bias of the alkyne assists iodocyclization, i.e., the methyl sulfide is a more powerful electron donor than the thiophene ring. Thus, the favourable electronic bias inherent in the ethynyl methyl sulfide systems, which has facilitated the sequence **4b**→**7b**→

24, augurs well for the synthesis of more extended oligomers.

We were also keen to see if the iodocyclization of less electron-rich alkynes could still be performed on these more extensively fused systems. Thus, Sonogashira coupling of **24** with phenylacetylene was undertaken to give **25** (88%). Again, addition of iodine to **25** produced a diiodoalkene (not shown) that required heating for conversion to **26** by the reversible pathway outlined in Scheme 2. Our usual reaction conditions for this, Conditions **A** (I_2 1.2 equiv., DCE, 80 °C), did not give a clean conversion to **26** (estimated to be $<40\%$ by ^{1}H NMR) and was accompanied by significant decomposition (Scheme 6). Assuming this to arise from the oxidative action of iodine on the extended π-system in **26**, we sought to address this by reducing the iodine to 1.0 equivalent (Conditions **B**). This significantly reduced decomposition but invariably reduced conversion levels, requiring further addition of iodine (20 mol%) and continued heating. In this way a good yield of **26** (85%) could be obtained. To better balance the opposing considerations of the redox sensitivity of **26** to iodine and the preference for an excess of iodine for complete conversion, we used a combination of an excess of iodine (1.3 equivalents) and 0.3 equivalents of TBAI (Conditions **C**). We rationalized that the TBAI (0.3 equiv.) would convert the 0.3 equivalents of excess of iodine to $TBAI_3$ (reversibly) and that this would provide a less volatile and less oxidative source of iodine, enabling the reaction to be driven to completion. This proved to be the case and **26** was obtained in near quantitative yield (99%) in good purity without chromatography [overall 41% yield from 2-iodothioanisole (**4b**)].[13]

In conclusion, a reiterative coupling (EMSS)/iodocyclization sequence has been developed and applied to the synthesis of some valuable thieno-fused heterocycles. In the course of this effort, strategies for overcoming unfavourable electronic bias and redox sensitivity have been developed that may prove useful elsewhere. Moreover, the synthetic approaches described in this work should provide a useful basis upon which to further explore the utility of thieno-fused heterocycles in materials design and bioactive discovery.

Experimental Section

Typical Procedure for the EMSS/Iodocyclization Sequence: Conversion of 17 to 20

Trimethyl orthobenzoate (1.89 mL, 11 mmol) and *p*-toluenesulphonic acid (100 mg, 0.58 mmol) were added to a suspension of 2-iodoaniline (2.19 g, 10 mmol) in toluene (40 mL) and the mixture stirred at reflux for 16 h. After cooling, the mixture was concentrated to a residue and then taken up in diethyl ether (50 mL), washed with saturated $NaHCO_3$ (30 mL) and dried over $MgSO_4$. The organic layer was filtered through a silica pad and eluted with diethyl ether. The organic layer was concentrated to an amber oil providing the benzimidate **17** in good purity; yield: 3.40 g (100%). The spectral properties were identical to those previously reported.[11]

This sample of **17** was taken up in THF:Et_3N (45 mL, 2:1), $Pd(PPh_3)_2Cl_2$ (3 mol%, 211 mg) and CuI (8 mol%, 152 mg), N_2 was then bubbled through the stirred mixture for 10 min. Then trimethylsilylacetylene (15 mmol, 2.12 mL) was added dropwise (5 min) and the mixture left to stir at room temperature overnight. The mixture was filtered and the filtrate concentrated to a residue that was taken up in diethyl ether (100 mL) and washed with saturated NH_4Cl (50 mL), H_2O (3×50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to a brown/black resin (4.05 g). The crude material was chromatographed on silica gel eluting with 5% diethyl ether in petroleum spirits providing the coupled material, methyl (*Z*)-*N*-{2-[(trimethylsilyl)ethynyl]phenyl}benzimidate, as an amber oil; yield: 3.05 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.27 (m, 4H), 7.24–7.12 (m, 3H), 6.88 (td, $J = 7.6$, 1.1 Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 4.02 (s, 3H), 0.20 (s, 9H).

This oil (3.05 g, 9.92 mmol) was taken up in MeOH (30 mL) and KF (866 mg, 14.9 mmol) and stirred at room temperature overnight. The mixture was concentrated to remove volatiles, taken up in diethyl ether (100 mL) and washed with H_2O (2×50 mL) and finally with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated providing the desilylated material, (*Z*)-*N*-{2-[(trimethylsilyl)ethynyl]phenyl}benzimidate, in good purity as an amber oil; yield: 2.27 g (96%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (dd, $J = 7.7$, 1.4 Hz, 1H), 7.35–7.27 (m, 3H), 7.25–7.19 (m, 2H), 7.18–7.11 (m, 1H), 6.91 (td, $J = 7.6$, 1.2 Hz, 1H), 6.67 (dd, $J = 8.0$, 0.8 Hz, 1H), 4.02 (s, 3H), 3.12 (s, 1H).

This alkyne material was dissolved in anhydrous THF (25 mL) and cooled to −78 °C (acetone-dry ice) and *n*-BuLi (2.2 M in hexane, 4.54 mL, 10 mmol) was added dropwise and the reaction mixture allowed to stir at −78 °C for 0.75 h after completion of the addition. The cold bath (dry ice-acetone) was replaced with an ice-bath and neat *S*-methyl methanethiosulfonate (1.12 mL, 10.5 mmol) was added dropwise to the ice-cold mixture with immediate formation of a precipitate. The mixture was left to stir a further 2 h and then diluted with diethyl ether (100 mL) and quenched with H_2O (50 mL). The aqueous layer was discarded and the organic layer was washed with H_2O (2×100 mL) and finally brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated giving **18** (~90% pure by ^{1}H NMR) as light amber oil; yield: 3.0 g. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.27 (m, 4H), 7.25–7.19 (m, 2H), 7.11 (ddd, $J = 7.9$, 7.5, 1.5 Hz, 1H), 6.89 (td, $J = 7.6$, 1.2 Hz, 1H), 6.70 (dd, $J = 8.0$, 0.8 Hz, 1H), 4.02 (s, 3H), 2.41 (s, 3H).

This sample of **18** was taken up in anhydrous dichloromethane (28 mL) and cooled to 0 °C under an N_2 atmosphere. Iodine (2.54 g, 10 mmol) was added portionwise and the mixture left to warm to room temperature and stir for 3 h in the dark. The reaction was then quenched with 10% $Na_2S_2O_3$ (120 mL). The organic layer was removed and the aqueous layer extracted with dichloromethane (40 mL). The

combined organic layers were dried ($MgSO_4$), filtered and concentrated to a brown/red viscous oil. The crude material was chromatographed on silica gel eluting with 5% diethyl ether in petroleum spirits, providing **20** as a viscous amber oil; yield: 3.74 g (7.79 mmol, 78% from 2-iodoaniline). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$–7.68 (m, 2H), 7.68–7.61 (m, 1H), 7.53–7.44 (m, 3H), 7.33–7.26 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 169.2$, 137.9, 135.7, 135.1, 133.7, 131.3, 130.2, 128.9, 126.0, 123.5, 122.1, 113.9, 82.8, 20.6. LC-MS: R_f (min) = 7.48; MS: $m/z = 394.0$ (M+H); HR-MS (ESI): $m/z = 415.9575$, calcd. for $C_{16}H_{12}INNaOS^+$ (M+Na): 415.9576.

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