An Efficient Approach toward 2,3-Dimethylene Pyrroles. Preparation and Reactions of Pyrrolo-3-sulfolenes

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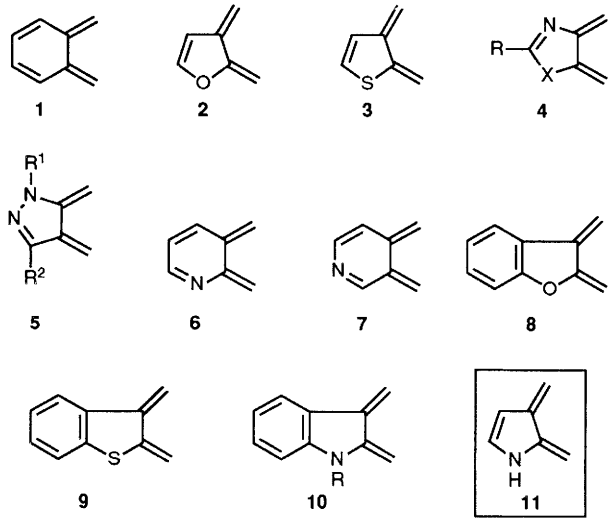
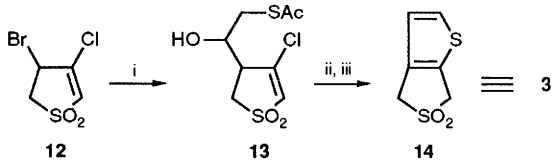
A new route has been developed toward the preparation of pyrrolo-3-sulfolenes, which can be used to generate the corresponding 2,3-dimethylene pyrroles, and their cycloaddition and substitution reactions have been successfully performed.

Recently, there has been an increasing interest in the study of the preparation and properties of 2,3-dimethylene heteroaromatics (DMHAs) which are analogues of orthoquinodimethane **1**.[1] Although many of this class of reactive compounds are known, *e.g.* the five-membered DMHAs **2**,[2] **3**,[3] **4** (X = O, S, NR),[4] **5**,[5] 2,3-dimethylene pyridines **6**,[6] **7**,[7] and the benzo-fused DMHAs **8**,[8] **9**[9] and **10**,[10] only the derivatives of 2,3-dimethylene indole **10** have been utilized extensively in organic synthesis. Most of the DMHAs are prepared by flash vacuum pyrolysis or by 1,4-elimination reaction from suitable precursors. One limitation of these methods is the precursors for DMHAs are sometimes not easily accessible. This might be the reason why 2,3-dimethylene pyrrole **11** or its derivatives has not been reported in literature. A more serious limitation is that it is difficult to perform further synthetic manipulation since the DMHAs are generated only *in situ*.

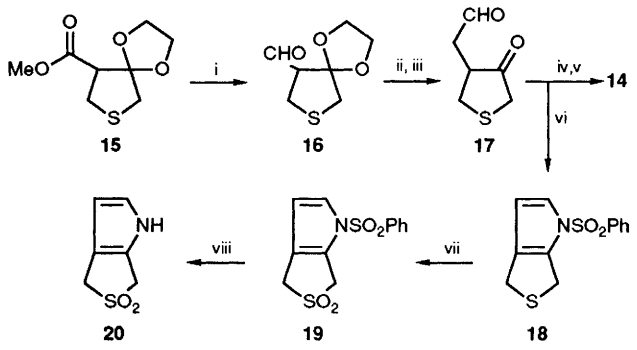


The preparation of a conjugated diene in the protected form as the corresponding 3-sulfolene has, among many, two important advantages.[11] On the one hand, the diene can be stereospecifically generated from the more stable 3-sulfolene under moderate conditions.[12] On the other hand, the diene can be activated by the sulfonyl group so that substitution at different positions can easily be achieved.[11,13] It is therefore preferable to prepare DMHAs *via* heterocycle-fused 3-sulfolenes. We recently reported a very concise approach for the preparation of **14**,[14] the precursor of 2,3-dimethylene thiophene **3** (Scheme 1) as well as its synthetic applications. We now describe a different route that efficiently yields the precursor of the so far unknown 2,3-dimethylene pyrrole **11**.

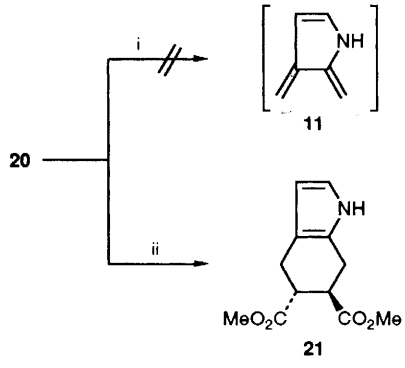
The synthetic route commenced with the readily available heterocyclic compound **15**[15] (Scheme 2). Reduction of **15** with DIBAL-H (diisobutylaluminium hydride) at −78 °C gave the ketal-aldehyde **16**. Homologation of the aldehyde functionality of **16** by a Wittig reaction followed by acidic hydrolysis



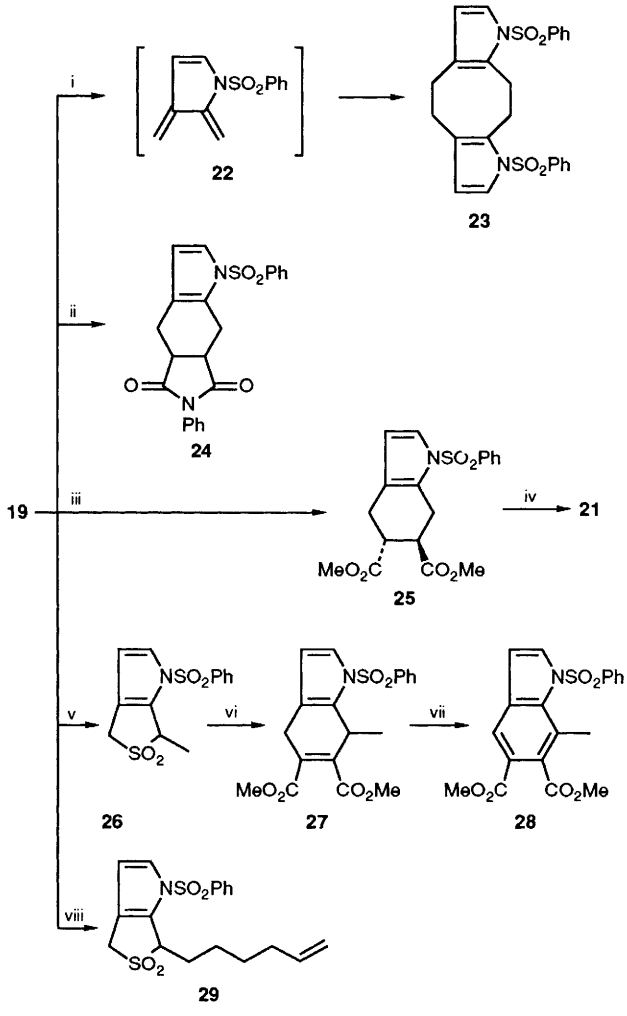
Scheme 1 *Reagents*: i, Zn, Ag, 2-(acetylthio)ethanal, ultrasound, toluene, 43%; ii, $NaHCO_3$, KCN, MeOH; iii, methylsulfonyl chloride, Et_3N, 49% from **13**



Scheme 2 *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, −78 °C, 70%; ii, $Ph_3PCH_2(OMe)Cl$, lithium diisopropylamide, tetrahydrofuran (THF), 0 °C, 83%; iii, 20% H_2SO_4, Et_2O, room temp., 78%; iv, Lawesson's reagent, toluene, reflux; v, $MeCO_3H$, room temp., 46% from **17**; vi, $PhSO_2NH_2$, *p*-TsOH, toluene, reflux, 70%; vii, MCPBA, CH_2Cl_2, room temp. 87%; viii, LiOMe, MeOH–THF, room temp., 44%



Scheme 3 *Reagents and conditions*: i, flash thermolysis; ii, dimethyl fumarate, sealed tube, 180 °C, acetone, 38%



Scheme 4 *Reagents and conditions*: i, 150 °C, toluene, 13%; ii, *N*-phenyl maleimide, 160 °C, toluene, 84%; iii, dimethyl fumarate, 160 °C, toluene, 95%; iv, Na–Hg, 63%; v, LiHMDS, MeI, THF–HMPA, −105 °C, 78%; vi, dimethyl acetylene dicarboxylate, 200 °C, toluene, 75%; vii, DDQ, toluene, reflux, 88%; viii, LiHMDS, 5-iodopent-1-ene, THF–HMPA, −105 °C, 81%; HMPA = hexamethylphosphoramide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

yielded the 1,4-dicarbonyl compound **17**. 1,4-Dicarbonyl compounds are versatile in the preparation of heterocyclic compounds. Indeed, treatment of **17** with Lawesson's reagent followed by peracetic acid oxidation gave the thieno-3-sulfolene **14**.[3c,14] When **17** was treated with phenylsulfonamide in the presence of a catalytic amount of TsOH (Ts = *p*-$MeC_6H_4SO_2$), the bicyclic heterocycle **18** was produced. Compound **18** could be oxidized to the pyrrolo-3-sulfolene **19** with *m*-chloroperbenzoic acid (MCPBA) or peracetic acid. Compound **19** is a stable solid that can be stored in a refrigerator for several weeks without appreciable decomposition.

Treatment of compound **19** with lithium methoxide (freshly prepared in MeOH by adding Bu^nLi) gave the unsubstituted pyrrolo-3-sulfolene **20** [^1H NMR (200 MHz in [$^2H_6$]acetone) δ 4.13 (s, 2H), 4.19 (s, 2H), 6.06 (m, 1H), 10.30 (brs, 1H)]. Compound **20** readily decomposed to a brown-coloured material when exposed to air. Attempted thermolysis of compound **20** failed to give DMHA **11** at various temperatures from 200 to 400 °C through a vertical hot tube. Nevertheless, the cycloadduct **21** could be obtained in 38% yield by reacting compound **20** directly with dimethyl fumarate in a sealed tube at 180 °C (Scheme 3). This result indicates that the DMHA **11** should have been generated and was trapped *in situ*. However, the low yield of the formation of **21** and the instability of **20** limit its synthetic usefulness.

Since compound **19** is much more stable than **20** and since the phenylsulfonyl group can be readily removed, compound **19** should be a better synthetic equivalent of **11** than **20**. In a test experiment, a toluene solution of **19** was heated at reflux where SO_2 was extruded and a [4 + 4] dimer **23** was formed (Scheme 4). Presumably the DMHA **22** was the intermediate. The reaction of **19** with a dienophile, *N*-phenyl maleimide or dimethyl fumarate, in a sealed tube at 160 °C gave the [4 + 2] cycloadduct **24** or **25**, respectively. Desulfonylation of **25** with Na–Hg gave compound **21**. The formation of **21** from **19** *via* the reaction sequence of Diels–Alder reaction and desulfonylation illustrates the synthetic equivalency of **19** and **11**.

Containing a 3-sulfolene functionality, compound **19** could be manipulated to give substituted derivatives. Treatment of **19** with lithium hexamethyldisilazide (LiHMDS) in the presence of MeI or 5-iodopent-1-ene produced the alkylated 3-sulfolene **26** or **29**, respectively. The deprotonation–alkylation reaction of **19** is highly regioselective so that the substitution takes place only at the α-position closer to the pyrrole-nitrogen atom. Isomers from alkylation at other positions of **19** were not obtained. A similar high regioselectivity has been observed in the substitution reactions of compound **14**.[14] The regioselective substitution reaction broadens the synthetic applications of 2,3-dimethylene pyrroles. For example, the reaction of **26** with dimethyl acetylenedicarboxylate at 200 °C resulted in the formation of the cycloadduct **28** which was aromatized to the highly functionalized indole **29**.

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