SYNTHESES OF 4-SUBSTITUTED 3,5-DIHYDRO-1*H*-THIENO[3,4-*c*]-PYRROLE 2,2-DIOXIDES AND THEIR DIELS-ALDER REACTIONS

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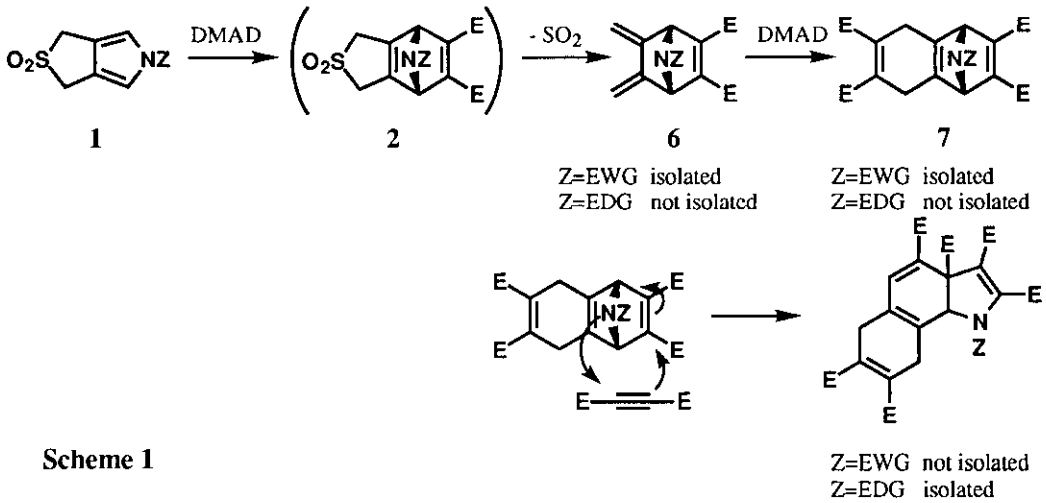
Abstract - The preparation of 4-substituted 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides and their intermolecular Diels-Alder reactions with DMAD are described. In the reaction with DMAD, 4-acetyl-3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides acted as the corresponding 3,4-dimethylenepyrroles.

In the course of our studies on the chemistry of 3-sulfolene,[1] we have been interested in five-membered heteroaromatic ring-fused 3-sulfolenes[2] and have performed the general synthesis of pyrrole-fused 3-sulfolenes, 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides (**1**).[3] These compounds contain pyrrole rings and 3-sulfolene moieties, which sequentially react with dienophiles to construct many types of interesting skeletons, depending on *N*-substituents, the dienophiles and the reaction conditions (Scheme 1).[3] Furthermore, pyrrolesulfolenes containing terminal olefin substituents undergo facile intramolecular Diels-Alder reaction and subsequent spontaneous desulfonylation to give the corresponding tricyclic framework in good yields, whereas the corresponding pyrroles do not.[4]



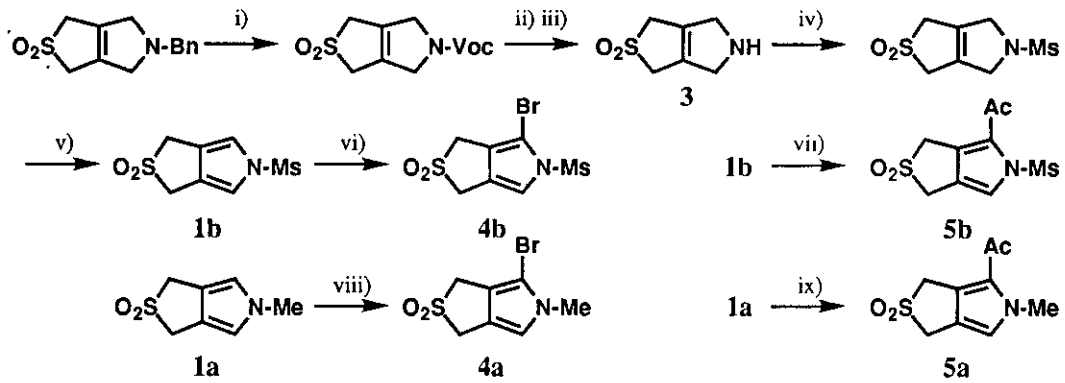
Scheme 1

In view of the well-known low reactivity of pyrroles as dienes and the inherent thermodynamic instability of their cycloaddition with alkenes (due to either retrocycloaddition or retro-Mannich reactions and rearomatization),[5] it is noteworthy that the intermolecular Diels-Alder adducts of pyrroles can be isolated

in good yields even under thermal conditions. The key to make the equilibrium favorable for product formation is rapid SO_2 extrusion from the initially formed adducts (**2**). Thus, the pyrrolesulfolenes are useful building blocks for the construction of polycyclic and polyfunctional systems. As continuation of our studies on the chemistry of pyrrolesulfolenes for the syntheses of variously substituted multicyclic molecules, we investigated the reactivity of their pyrrole moieties having both *N*-substituents (the methyl group as an increasing aromaticity and the methanesulfonyl group as a decreasing one) and α-substituents (acethyl and bromide). In this paper, we report the preparation of *N*,4-disubstituted pyrrolesulfolenes (**4**) and (**5**) and the results of their Diels-Alder reactions.

Modification of the pyrrole-ring

N-Methanesulfonylpyrrolesulfolene (**1b**) was synthesized from 3,4,5,6-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (**3**) by the reported method.[3a, 4] In this study, the key compound (**3**) was prepared *via* the *N*-dealkylation of *N*-benzylpyrrolinesulfolene with vinyl chloroformate (Scheme 2), because α-chloroethyl chloroformate, the *N*-dealkylation reagent,[6] is not commercially available. This modified route has enough advantages to provide the excellent overall yield (82.7%) of **3** from *N*-benzylpyrrolinesulfolene (68.2%, the earlier method[3a]).



Scheme 2 *Reagents and conditions:* i, Voc-Cl, 1,2-dichloroethane, 0 °C; ii, Br_2, dichloromethane, -15 °C; iii, MeOH, 50 °C; iv, Ms-Cl, pyridine, 0 °C, 71.3%; v, chemical MnO_2 (40 mol-equiv.), dichloromethane, rt, 80.6%; vi, NBS (3.3 mol-equiv.), THF, rt, 76.8% ; vii, Ac_2O (2.2 mol-equiv.), BF_3•Et_2O (4.4 mol-equiv), 1,2-dichloroethane, rt; viii, NBS (0.9 mol-equiv), THF, -78 °C ; ix, Ac_2O (1.1 mol-equiv.), BF_3•Et_2O (2.2 mol-equiv), 1,2-dichloroethane, rt.

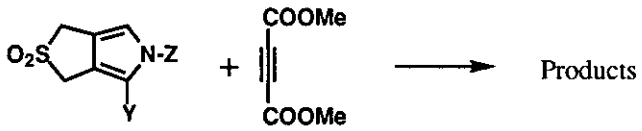
Bromination of *N*-methylpyrrolesulfolene (**1a**)[3a] with NBS in THF at room temperature gave the dibromide as a single product in 99.6% yield (2 mol-equiv. of NBS was needed to consume **1a**). The best yield (73.9% based on consumed **1a**) of the 4-bromopyrrolesulfolene (**4a**) was obtained on treating **1a** with 0.9 mol-equiv. of NBS at -78 °C (18.3% of **1a** was recovered). Treatment of **1a** with Ac_2O (1.1 mol-equiv.) in the presence of $BF_3 \cdot Et_2O$ (2.2 mol-equiv.) in 1,2-dichloroethane afforded 4-acetylpyrrolesulfolenes (**5a**) (91.2%). Treatment of **1b** with 2.2 mol-equiv. of Ac_2O and 4.4 mol-equiv. of $BF_3 \cdot Et_2O$ gave **5b** in 83.9% yield. The structures of all new pyrrolesulfolenes were confirmed by spectral data.

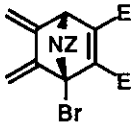
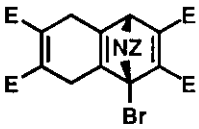
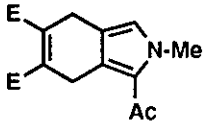
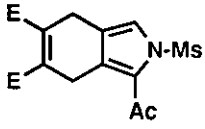
Diels-Alder reaction of the 4-substituted pyrrolesulfolenes

In the case of 4-bromopyrrolesulforenes, *N*-methanesulfonylpyrrolesulfolene (**4b**), of which the aromaticity is reduced by the methanesulfonyl group on the nitrogen atom, reacted with 3 mol-equiv. of dimethyl

acetylenedicarboxylate (DMAD) at 170 °C for 24 h to give the bis-cycloadduct (**7b**) in 41.5% yield (Table). Interestingly, the Diels-Alder reaction of *N*-methyl-4-bromopyrrolesulfolene (**4a**) with DMAD took place at 170 °C (2.5 h) to afford the monocycloadduct (**6a**) bearing two methylene groups in 36.2% yield.

Table Diels-Alder reaction of *N*,4-disubstituted pyrrolesulfolenes with DMAD (3 mol-equiv.)

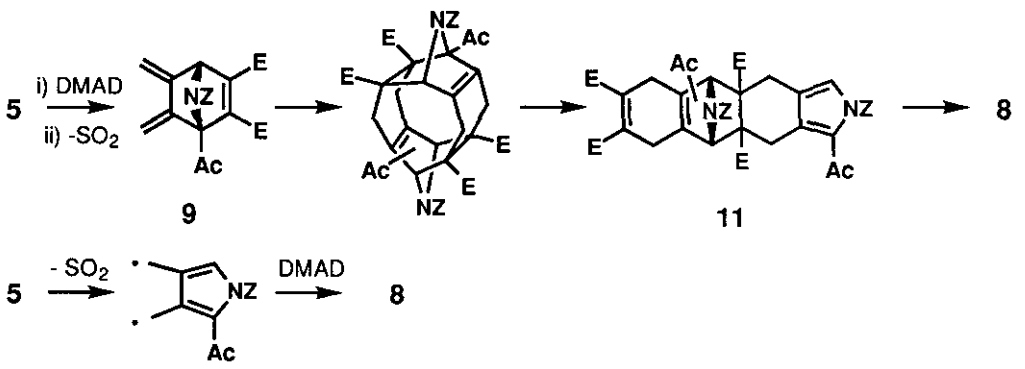


Pyrrolesulfolene	Reaction conditions	Products	
4a (Y=Br, Z=Me)	sealed tube, 170 °C 2.5 h, benzene		**6a** (Z=Me, E=COOMe) 36.2%
4b (Y=Br, Z=Ms)	sealed tube, 170 °C 24 h, benzene		**7b** (Z=Ms, E=COOMe) 41 5%
5a (Y=Ac, Z=Me)	sealed tube, 170 °C 24 h, benzene		**8a** (E=COOMe) 77.7%[a]
5b (Y=Ac, Z=Ms)	sealed tube, 200 °C 24 h, benzene		**8b** (E=COOMe) 29.7%[b]

a) The yield was based on consumed **5a** and 63.2% of **5a** was recovered. b) The yield was based on consumed **5b** and 32.6% of **5b** was recovered.

On the other hand, 4-acetylpyrrolesulfolenes (**5a**) and (**5b**) gave new type of 1 :1 cycloadducts (**8a**) and (**8b**) independent on the nature of the *N*-substituents. *N*-Methyl-4-acetylpyrrolesulfolene (**5a**) reacted with DMAD at 170 °C (24 h) to afford **8a** in 77.7% yield (based on consumed **5a**: 63.2% of **5a** was recovered). The reaction of **5b** with DMAD required the heating at 200 °C for 24 h and gave **8b** in 29.2% (based on consumed **5b**: 32.6% of **5b** was recovered).

Formation of **8** may be considered in terms of a reaction pathway *via* **9** or that *via* the 3,4-dimethylenepyrrole (**10**) (Scheme 3). The former is as follows: a Diels-Alder reaction first occurs on the pyrrole moiety of **5** to give a 7-azanorbornyl ring fused 3-sulfolene, from which sulfur dioxide is eliminated instantaneously to give **9**; two molecules of **9** undergo an intermolecular Diels-Alder reaction to afford a cyclic dimer, which is then converted a linear dimer (**11**); a retro-Diels-Alder reaction of this linear dimer then affords **8**. This mechanism is in accord to the results of both the reaction of 1-acetyl-4*H*,6*H*-dihydrothieno[3,4-*c*]furan 5,5-dioxide (acetylfuransulfolene) with DMAD[2e, 2k] and the retro Diels-Alder reaction of 7-azanorbornadienes (**7**) which are thermally stable and give no **8**.



Scheme 3

As for the possibility of the latter, we calculated the MOs of **5a** and **5b** by the extended Hückel method on CAChe system.[7] The calculations showed that both the HOMOs and the LUMOs of **5** are not dienic but HOMO-1s are dienic, whereas the HOMOs of 4-bromopyrrolesulfolenes (**4a**) and (**4b**) are dienic. These results support the possibility of the latter reaction pathway.

Yields have not yet been optimized, the Diels-Alder reactions of **1** can be controlled by the choice of the combination of *N*- and α-substituents on the pyrrole ring of **1**. This method should be fruitful in constructing a number of polycyclic polyfunctional aza-systems.

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