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Type One and Type Two Intramolecular Diels–Alder Reactions of Quinolono-*o*-quinodimethanes

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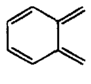
Abstract: Substituted quinolono-*o*-quinodimethanes have been generated from quinolone-fused 3-sulfolenes by thermolysis. These transient intermediates undergo smooth type one and type two intramolecular Diels–Alder reactions to produce linearly fused and bridged multicyclic heterocycles.

Whereas a tremendous amount of research interests have been focused on the chemistry of *o*-quinodimethane (QDM) **1** and its derivatives for more than forty years,[1] the heteroaromatic analogues have drawn the notice of organic chemists only more recently.[2] Heteroaromatic *o*-quinodimethane (HAQDM) **2** can be generated by several methods, among which the strategy of using extrusion of sulfur dioxide from heterocycle-fused 3-sulfolenes **3** appears most ideal for synthetic applications.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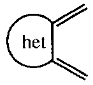

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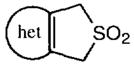

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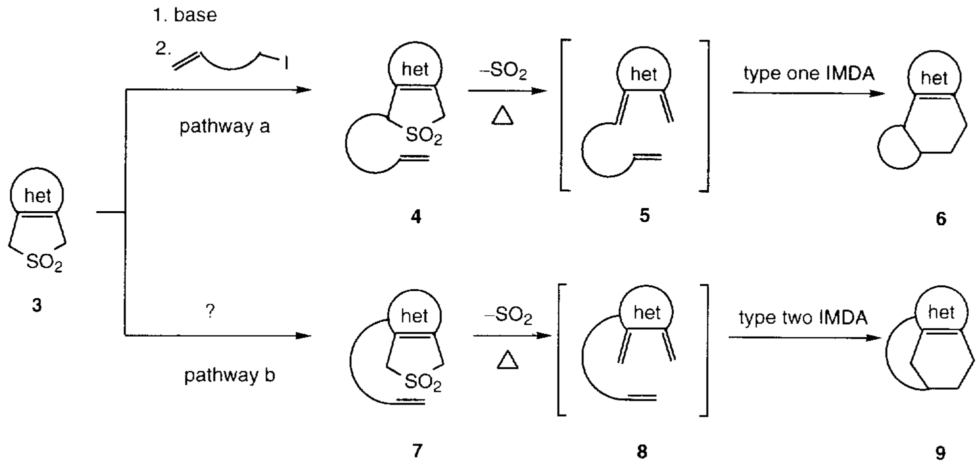
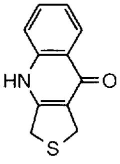
One of the greatest advantages of using 3-sulfolenes as precursors for the corresponding conjugated dienes or QDM's is the ease of introducing substituents, and thus functionalities, at the α-position of the sulfone group, leading to various derivatives.[3] This strategy has been applied in synthesis of compound **4** of which the thermal extrusion of sulfur dioxide and subsequent type one intramolecular Diels–Alder (IMDA) reaction produce a multicyclic heteroaromatic **6** (Scheme I, pathway a).[4] In principle, a type two IMDA reaction[5] of compound **7** may take place upon thermolysis to produce a bridged multicyclic heteroaromatic compound **9** (Scheme I, pathway b). Although type two IMDA reactions have been known for more than a decade,[5] in all of the precursor molecules the dienophilic part connected at the 2-position of a conjugated diene is always an open chain. The type two IMDA reaction of HAQDM's is so far unknown and we considered it to be somewhat more difficult because of the less flexibility of the long chain in compound **8**.

Scheme I



Recently Storr[6] reported the synthesis of quinolone-fused 3-sulfolene **11** and its quinoline analogues **12** from **10** and the thermal reactions of these compounds. It was found that **12** could not be converted to the QDM's **14** upon heating, whereas quinolono-QDM such as **13** could be generated from **11** with great case. Since compounds **10–12** are all convenient to prepare on large scale, we chose this system as a model to study the type one and type two IMDA reactions of HAQDM's.



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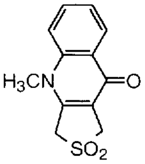

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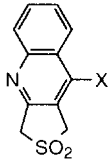

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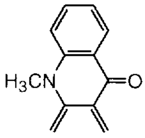

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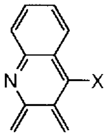

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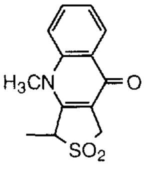
Type One Intramolecular Diels–Alder Reactions

The deprotonation/alkylation reactions of 3-sulfolenes are usually performed at −78 °C or −105 °C in THF using BuLi or LiHMDS as the base.[3] However, these conditions could not be exercised on compound **11** because of its low solubility in THF. Therefore, a different reaction condition was explored where compound **11** was treated with NaH in DMF at 0 °C followed by the addition of excess of MeI. The reaction was highly regioselective to give the monomethylated product **15** in 70% yield. The introduction of two methyl groups could be achieved in one pot using two equivalents of NaH where compound **16** was obtained in 76% yield. Substitution of **11** with 5-iodo-1-pentene under similar conditions gave product **17** in 39% yield.



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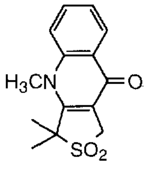

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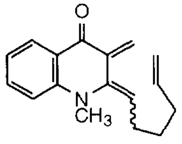

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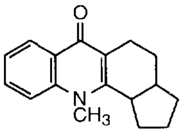

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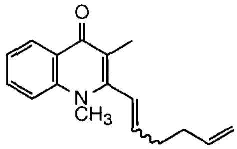

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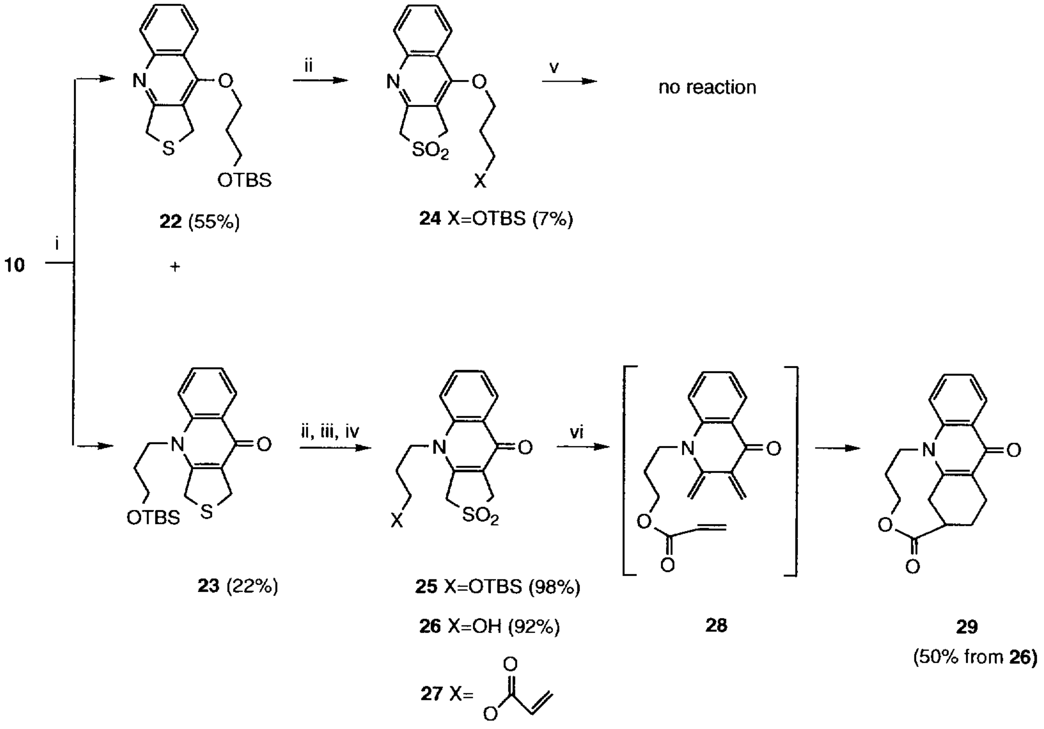
Thermolysis of **17** at 200 °C in a sealed tube produced a mixture of **19** (22%) and **20** (41%). The formation of **19** indicates the successful generation of the intermediate HAQDM **18** and the subsequent type one IMDA reaction. Although the yield for **19** was only moderate, the route constitutes a straight-forward approach to a tetracyclic compound containing quinolone moiety. Compound **20** is a result of the 1,5-H shift reaction of **18**. The competition between IMDA reaction and 1,5-H shift reaction is often observed in systems involving QDM's.[7]

Type Two Intramolecular Diels–Alder Reactions

In order to test the feasibility of type two IMDA reactions on the quinolono-QDM systems, the dienophile-containing chain needs to be introduced at either the nitrogen or the oxygen atom of the quinolone ring. Thus, compound **10** was deprotonated with NaH/DMF followed by treatment with the siloxyiodopropane **21** where a mixture of *O*-substituted product **22** and *N*-substituted product **23** was obtained. Oxidation of **22** with mCPBA gave the corresponding 3-sulfolene **24** in very low yield. Such difficulty was not unprecedented. Storr failed to obtain **12** (X=Cl) from the direct oxidation of the corresponding sulfide.[6] Heating compound **24** at 300 °C for 1 h resulted only in recovered starting material indicating that the thermal removal of SO_2 from **24** is as difficult as from **12**.[6] In sharp contrast, oxidation of **23** with mCPBA was extremely easy and **25** was formed in nearly quantitative yield. Desilylation of **25** with HOAc and subsequent esterification of the intermediate alcohol **26** with acryloyl chloride provided the desired target compound **27** (Scheme II). Attempted purification of **27** by column chromatography resulted in substantial decomposition. Therefore, compound **27** was used without purification. Thermolysis of the crude **27** at 210 °C for 30 min gave the cycloadduct **29** illustrating the first successful type two IMDA reaction on a QDM system such as **28**. This approach allows chemists to prepare bridged multicyclic heterocycles efficiently.

Scheme II



Reagents and conditions: (i) NaH/DMF, 0 °C, $ICH_2CH_2CH_2OTBS$ (**21**); (ii) mCPBA/CH_2Cl_2, 0 °C; (iii) AcOH/H_2O/THF (3:1:1), room temp.; (iv) CH=CHCOCl, NEt_3, CH_2Cl_2, 0 °C; (v) CH_3CN, 300 °C, 1 h; (vi) CH_3CN, 210 °C, 30 min.

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