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Expeditious synthesis of the aromatic spiroketal skeleton using hetero-Diels–Alder cycloaddition

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Abstract—The hetero-Diels–Alder reactions of enolic ethers generated from methylenation of various esters are described, which allow for the rapid synthesis of various substituted [6,6] aromatic spiroketal skeletons.

Aliphatic spiroketals have attracted much attention, and there are many examples for the synthesis of the non-anomeric structures.[1] However, the aromatic spiroketal skeletons, which are found in a broad range of bioactive natural products such as heliquinomycin (**1**) and its analogues (Fig. 1),[2] remain a formidable challenge despite the progress, which has been achieved in this area in the recent years.[3] Our interest in the structures of diverse aromatic spiroketal skeletons promoted us to consider methods for expeditious synthesis of these molecules. The synthesis of aliphatic spiroketals using hetero-Diels–Alder reactions have been explored by Pzul in 1954.[4] *o*-Quinone methides are known to react with a range of dienophiles to perform [4+2] cycloaddition.[5] To our knowledge, the use of hetero-Diels–Alder reaction for the synthesis of the aromatic spiroketal skeletons such as **A** has not previously been reported (Fig. 2). We envisioned that the aromatic spiroketal skeleton **A** could arise from a cycloaddition between the *o*-quinone methides **B** and the enolic ethers **C** or **D**. In this letter, we wish to report our results on the rapid synthesis of various substituted [6,6] aromatic spiroketal skeletons by using hetero-Diels–Alder reactions.

o-Quinone methides are extremely reactive transient species, undergoing dimerization or trimerization in the absence of a nucleophile or electron-rich alkene.[6] There are many strategies, which have been established in order to generate *o*-quinone methides in situ in the past years.[7]

Because of our experience with *o*-quinone methide reactivity, we firstly examined their capacity of reacting with commercially available ethoxyethene (**8**). Initially, the *o*-quinone methides for the reaction were prepared on the basis of the simple protocol described by Bolon.[7a] As shown in Figure 3, to generate the *o*-quinone methide from *o*-cresol (**7**), oxidation reagent Ag_2O was added, then ethoxyethene was mixed at room temperature, but no product was found. Using 2-methylbenzene-1,4-diol (**10**) as *o*-quinone methide precursor, 2-methylcyclohexa-2,5-diene-1,4-dione (**11**) was obtained in 80% yield.

Very recently, a new and efficient method for *o*-quinone methides intermediate generation from *o*-methyleneacetoxy-phenols has been developed and applied by Baldwin.[5h] Based on this methodology, *o*-quinone methides precursor were prepared. The syntheses of *o*-quinone methides precursor was started from commercially available *o*-hydroxybenzaldehyde (**12** or **13**). The corresponding aldehydes **14** and **15** were readily prepared by acylation of *o*-hydroxybenzaldehyde (**12** or **13**) with Ac_2O in the presence of K_2CO_3 in ethyl ether. The conversion of the aldehyde (**14** or **15**) to the *o*-quinone methides precursor (**16** or **17**) was realized by using borane–DMS complex reduction (Scheme 1).

o-Quinone methides generated in the presence of the ethoxyethene lead to cycloaddition, adduct **18** (Table 1), which thus verifies the Baldwin's methodology. After optimization of the reaction time and temperature cycloaddition adduct **18** was obtained in 60% yield.

Enolic ethers **D** for the reaction can be readily prepared on the basis of the protocol described in the literature.[8]

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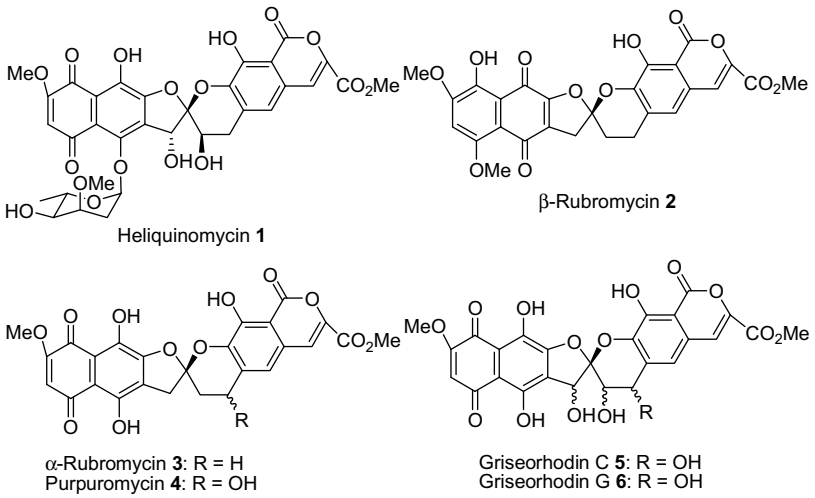


Figure 1. Examples of biologically active aromatic spiroketal.

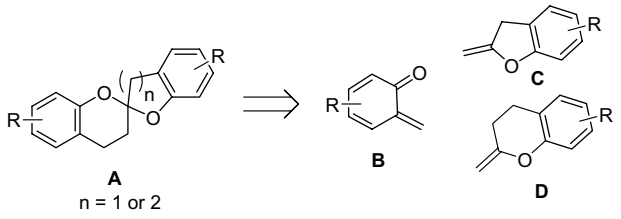


Figure 2. Proposed construction of the aromatic spiroketal skeletons **A** by cycloaddition of the *o*-quinone methides **B** and the enolic ethers **C** or **D**.

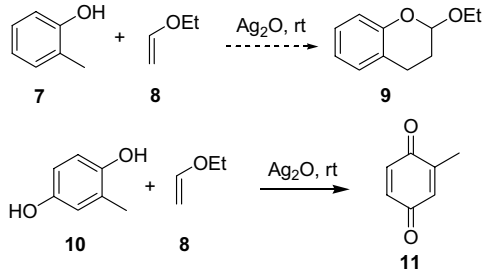
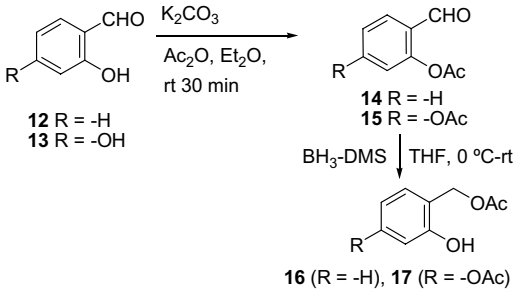


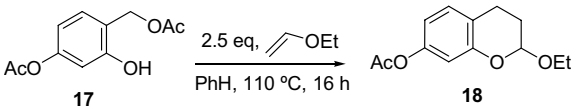
Figure 3. Using Bolon's protocol to generate the *o*-quinone methide.



Scheme 1. Preparation of *o*-quinone methides precursor.

Our studies then focused on the hetero-Diels–Alder cycloaddition between the *o*-quinone methides **B** and the enolic ethers **D**. As shown in Table 2, entry 1, in the case where no catalyst was used, the *o*-quinone methides precursor **17** and the enolic ethers **19** gave spiroketal product **24a** as a single regioisomer in 59% yield; the addition of $TiCl_4$ as catalyst improved the yield to 71%. Variation of enolic ethers **D** was carried out. Results (entries 2–5) suggest that the yield of spiroketal product was not significantly affected by the enolic ethers.[9] Using compound **16** as the *o*-quinone methides precursor, the yield of spiroketal products was slightly decreased (entries 6 and 7).

Table 1. Cycloaddition of 2-acetoxymethyl-5-acetoxyphenol with ethoxyethene

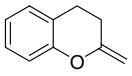
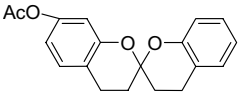
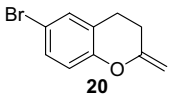
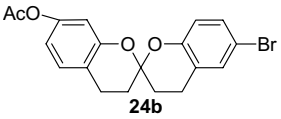
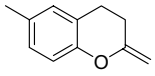
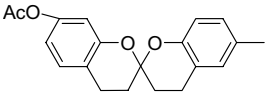
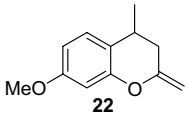
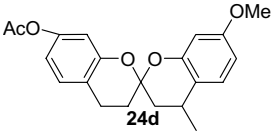
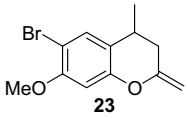
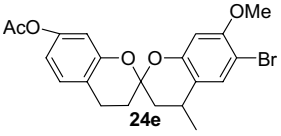
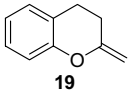
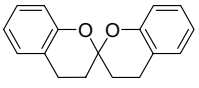
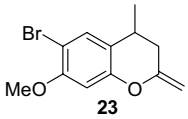
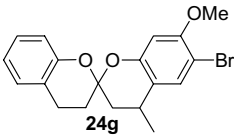


Entry	Time (h)	Temperature (°C)	Yield (%)
1	10	110	52
2	16	110	60
3	24	110	60
4	24	130	60

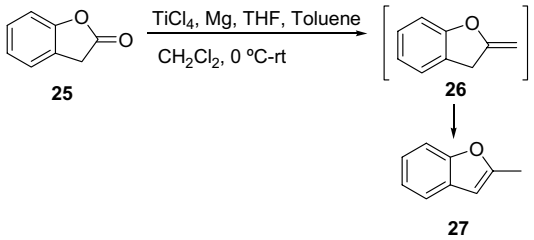
In order to further explore the versatility of this cycloaddition, we tried to synthesize various substituted [5,6] aromatic spiroketal skeletons by hetero-Diels–Alder reactions. The synthesis of enolic ethers such as **C** was carried out using Yan's methodology.[8] Unfortunately, methylenation with benzofuran-2(3*H*)-one (**25**) under the standard conditions gave an olefin isomerization product **27**, which is believed to be derived from the normal product **26** (Scheme 2). Now the synthesis of the enolic ethers such as **26** is under process.

In conclusion, the hetero-Diels–Alder reactions of enolic ethers generated from methylenation of various esters are described, which allow for the rapid synthesis of various substituted [6,6] aromatic spiroketal skeletons. These heterocyclic compounds may be prove to be medically interesting molecules in the future.

Table 2. Cycloaddition of the *o*-quinone methides precursor **C** with enolic ethers **D**

Entry	*o*-Quinone methides precursor	Enolic ethers	Spiroketal product	Yield (%)[a]
1	**17**	 **19**	 **24a**	59[b] 71[c]
2	**17**	 **20**	 **24b**	48
3	**17**	 **21**	 **24c**	58[b] 70[c]
4	**17**	 **22**	 **24d**	60[b] 73[c]
5	**17**	 **23**	 **24e**	59
6	**16**	 **19**	 **24f**	51
7	**16**	 **23**	 **24g**	47

[a] Yields were calculated after column chromatography.
[b] Yield obtained without any catalyst.
[c] Yield obtained by the catalysis of $TiCl_4$.



Scheme 2. Preparation of the enolic ethers such as **C**.

Acknowledgements

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9. Typical procedure for the synthesis of the aromatic spiroketals: In a sealed tube was stirred 6-bromo-3,4-dihydro-2-methylene-2*H*-benzopyran (112.0 mg, 0.50 mmol) with 2-acetoxymethyl-5-acetoxyphenol (**17**) (112.0 mg, 0.50 mmol) in benzene (1.0 mL) at 110 °C under argon for 28 h. After evaporation of benzene under reduced pressure, the colourless oil obtained was purified by flash silica gel chromatography (16:1 30–60 P.E.:EtOAc) to give a white solid (90.1 mg, 48%) of spiroacetal (**24b**). Mp 123–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.25 (d, 1H), 7.09–7.17 (m, 2H), 6.59–6.65 (m, 2H), 6.49 (d, $J = 2.1$ Hz, 1H), 3.17–3.23 (m, 2H), 2.68–2.76 (m, 2H), 2.24 (s, 3H), 2.17–2.21 (m, 2H), 1.90–2.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 20.4, 20.7, 21.1, 30.7, 30.9, 96.2, 110.4, 113.0, 114.2, 118.9, 119.7, 124.3, 129.5, 130.0, 131.5, 149.5, 151.1, 152.4, 169.6. MS (ESI) FW = 388.03, $m/z = 388.00$. HRMS calcd for $C_{19}H_{17}BrO_4$ ($M+NH_4^+$) 406.0648, found 406.0650.