Communications

A Synthesis of Trisquinones

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Received April 14, 1998

Exceptionally high and selective anti-HIV activity in a variety of cellular in vitro tests was reported for the trimeric naphthoquinone conocurvone (Figure 1).[1] Because teretifolione B, the monomer comprising the two noncentral quinone units of conocurvone, was devoid of antiviral activity, the observed biological activity was attributed to the trisquinone structure.[2] The development of a general synthetic entry to trisquinones (and oligoquinones) is therefore of considerable interest because it could lead to a new source of biologically active compounds.

Although a wide variety of quinones are known and quinone syntheses have been extensively reviewed,[3,4] very few oligoquinones have been reported.[5−7] The few approaches to oligoquinones that are documented suffer from very low overall yields and poor solubilities of the products. For example, in 1990, a light-sensitive trisnaphthoquinone was prepared in approximately 1% overall yield from commercially available starting materials.[5] Other simple oligobenzoquinones and their derivatives have also been reported,[7] but they are also unstable to varying degrees and are poorly soluble. To date, there is no competent and general synthetic approach to trisquinones.

In the past decade, a mild and general synthesis of substituted quinones was developed (Scheme 1).[8,9] It relies upon maleoyl- (**1**) or phthaloylcobalt (**2**) complexes that, depending upon the nature of the ligand "L" on cobalt, are activated either thermally or photochemically and react with a large variety of alkynes to give quinone complexes **3** in high yields. The intermediate cobalt−quinone π-complexes are readily demetalated, either directly under the reaction conditions or upon brief treatment with ceric ammonium nitrate (CAN). The mild reaction conditions and functional group compatibility of the maleoyl/phthaloylmetal procedure seemed ideally suited to the construction of sensitive trisquinones from alkynes that bear suitable quinone or quinone precursor substituents. This notion was reduced to practice, which established the first general synthetic route to substituted trisquinones. Although only symmetric trisquinones **4** were synthesized in this initial study, unsymmetrically substituted ones should also be available via this protocol.

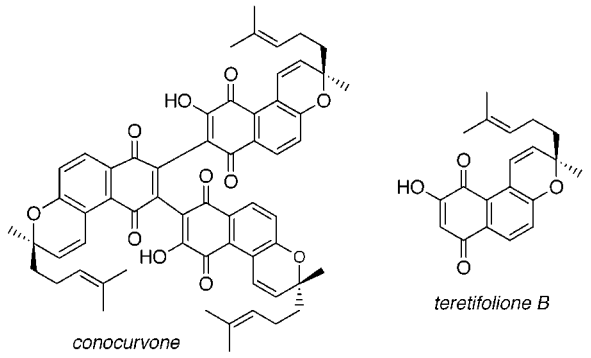
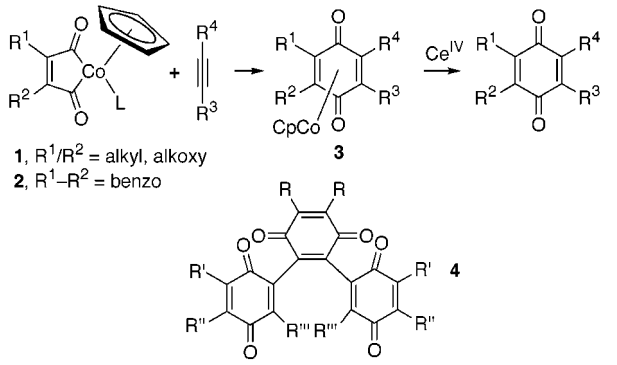


Figure 1.

Scheme 1



1,2-Diarylalkynes (**5a**−**e**, Table 1) were easily prepared from bis(tri-*n*-butylstannyl)acetylene and 2 equiv of the corresponding iodoarene using a cross-coupling procedure.[10] Reaction of diarylalkynes **5a**,**b**,**d** with maleoylcobalt complex **6** in 1,2-dichloroethane at 80 °C for 24 h in a sealed tube[8] provided the trisquinone precursor cobalt complexes **7a**,**b**,**d**, respectively, in high yields (Table 1). Photochemical activation of phthaloylcobalt complex **6′** in the presence of **5b**,**d**,**e** produced the trisquinone precursors **7b′**,**d′**,**e′**, respectively, which were directly isolated as the corresponding 2,3-diarylnaphthoquinones in good yields. In contrast to the robust CpCo(benzoquinone) complexes, spontaneous demetalation of the more weakly ligated CpCo(naphthoquinone) complexes is known to occur under the reaction conditions.[8] Both the cobalt complexes **7** and the demetalated 2,3-diarylnaphthoquinones show two sets of signals in their ^{1}H NMR spectra due to atropisomerism; coalescence of signals for demetalated **7d′** was not observed up to 120 °C in DMSO. The ^{13}C NMR spectra of the trisquinone precursors are also very complex, especially those with cobalt attached. This was not unexpected since the natural product conocurvone also exhibits spectral data complicated by atropisomerism.[1]

Following a literature procedure,[8] when **7a**,**b**,**d** were treated with 10 equiv of CAN at 0 °C for 30 min (for demetalation) and then at room temperature (for oxidative demethylation), complicated mixtures were formed. How-

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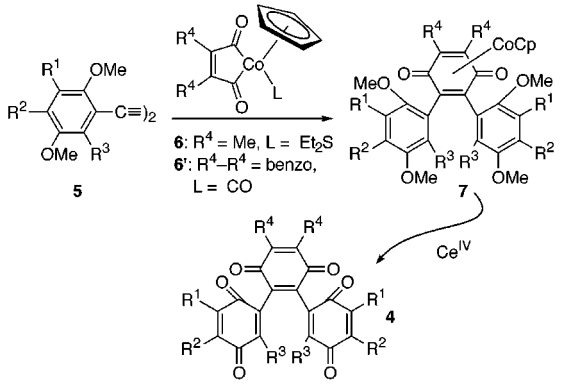
S0022-3263(98)00680-X CCC: $15.00
Published on Web 08/05/1998

Table 1. Syntheses of Trisquinones



Entry	Reactants[a]	R^1	R^2	R^3	R^4	Products (%)
1	**5a, 6**	H	H	H	Me, Me	**7a** (92); **4a** (86)
2	**5b, 6**	Me	Me	H	Me, Me	**7b** (82); **4b** (85)
3	**5b, 6'**	Me	Me	H	benzo	**7b'** (75)[b]; **4b'** (75)
4	**5c, 6**	Me	Me	Me	Me, Me	**7c** (0); **4c**[c]
5	**5d, 6**	benzo		H	Me, Me	**7d** (78); **4d** (75)
6	**5d, 6'**	benzo		H	benzo	**7d'** (68)[b]; **4d'** (80)
7	**5e, 6'**			H	benzo	**7e'** (61)[b]; **4e'** (78)
8	**5f, 6'**	benzo		OMe	benzo	**7f'** (0); **4f**[c]

[a] Reaction conditions. Maleoylcobalt complex **6**: 1,2-dichloroethane, 80 °C, 24 h. Phthaloylcobalt complex **6′**: 1,2-dichloroethane, UV irradiation, 25 °C, 36 h. Demetalation to the 2,3-diarylnaphthoquinone occurs under the reaction conditions. [b] Isolated as the demetalated 2,3-diarylnaphthoquinone. [c] Unavailable.

ever, when **7a**,**b**,**b′**,**d**,**d′**,**e′** were treated with 10 equiv of CAN at room temperature and subjected to workup *after 3 min*, the corresponding trisquinones **4a**,**b**,**b′**,**d**,**d′**,**e′** were isolated as yellow solids in high yields. Perhaps due to the increased steric hindrance about the triple bond, diarylalkynes **5c** and **5f** failed to react with cobalt complexes **6** and **6′**. Further studies are needed to probe the introduction of substituents $R^3 \neq H$ in **4**, as in the natural product conocurvone, since such substituents will stabilize the acyclic trisquinones from undesired cyclization.[11]

The trisquinones are yellow solids, soluble in organic solvents such as CH_2Cl_2, THF, and EtOAc. Upon exposure to air and light, the solids quickly darken, but the majority of the mass remains unchanged. Decomposition in solution is faster but still slow enough that chromatography or recrystallization can be carried out without noticeable decomposition. Unlike their precursors that displayed complicated NMR spectra due to atropisomerism in solution, all of the trisquinones showed a single set of NMR spectral signals. A broad peak was observed in the ^{1}H NMR spectra between 6.4 and 6.8 ppm, which is typical of the quinone ring C−H, and absorbances were seen between 182 and 186 ppm for the carbonyl carbons in the ^{13}C NMR spectra. One or two very strong absorptions were observed in the carbonyl region of the IR spectra (1654−1673 cm^{-1}). The ^{1}H NMR and IR spectra and the melting point of the known trisnaphthoquinone **4d′** were in agreement with the data reported in the literature.[5]

In conclusion, a simple and mild new method for the synthesis of trisquinones has been developed. The compounds prepared in this study have been submitted for biological assay.

Acknowledgment. This investigation was supported by Grant No. CA40157, awarded by the National Cancer Institute, DHHS. We also acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health, S10-RR-02478.

Supporting Information Available: A complete description of the synthesis and characterization of all compounds in the manuscript (50 pages).

JO980680C

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