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Tetrahedron
Tetrahedron 62 (2006) 10344–10351

Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones

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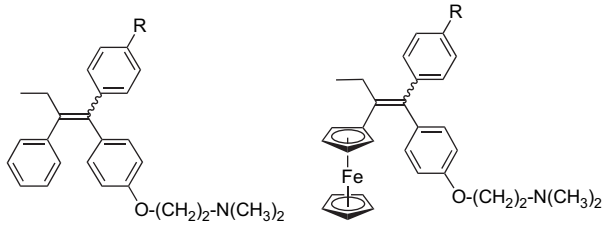
Received 13 June 2006; revised 6 August 2006; accepted 23 August 2006
Available online 11 September 2006

Abstract—A squarate-based synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones is described. When refluxed in dioxane at 100 °C, heated with silica gel as a solvent free grinded solid mixture at 125 °C or stirred with silica gel in ethyl acetate at room temperature, 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones, prepared from ethynylferrocene and 3-cyclobutene-1,2-diones, afforded 2-ferrocenylidene-4-cyclopentene-1,3-diones as the major or single product of the reaction. In some cases, ferrocenyl quinones also resulted from these reactions as the minor products. The major or exclusive formation of 2-ferrocenylidene-4-cyclopentene-1,3-diones is attributed to the radical-stabilizing ability of the ferrocenyl group.

1. Introduction

The great interest in ferrocenyl-substituted organic compounds is associated both with the peculiar chemical behavior of the ferrocene systems and with the unusual properties it imparts on the organic moiety.[1] Due to its unique structure, different membrane-permeation properties, and anomalous metabolism, ferrocene is often incorporated into a compound in order to obtain unexpected or enhanced biological activities.[2,3] A successful example is hydroxyferrocifen, which was obtained by replacing the phenyl ring of hydroxytamoxifen by a ferrocenyl group (Fig. 1).[3] Hydroxyferrocifen is the first molecule shown to be active against both hormone-dependent and hormone-independent breast cancer cells.[3] In contrast, hydroxytamoxifen, the active metabolite of tamoxifen, is active only against hormone-dependent cancer cells.[4] Notably, the integration of a ferrocenyl group into the structure generates surprising antiproliferative effects on both type of cancer cells. It appears so far that ferrocene derivatives act via mechanisms different from those of cisplatin and thus may lend themselves to treatment of a wider range of cancers. In general, the antitumor effect of ferrocene compounds is attributed to the redox properties of the central iron atom, in that only the oxidation state +3 (as in ferrocenium cations), which is readily produced by biological oxidation, exhibits inhibitory effects.[5] Therefore, in recent years, considerable interest has been devoted to the synthesis of new ferrocene derivatives, which could be potential antitumor substances.[6,7]



Tamoxifen (R = H)
Hydroxytamoxifen (R = OH)

Ferrocifen (R = H)
Hydroxyferrocifen (R = OH)

Figure 1. Structures of tamoxifens and ferrocifens.

The rapid spread of cancer has sparked an intense chemical search for new structure leads, which may be of use in designing novel antitumor drugs. In this regard, the 2-methylene-4-cyclopentene-1,3-dione pharmacophore (**1**) has occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities (Fig. 2). Inayama and co-workers synthesized a series of 2-arylidene-4-cyclopentene-1,3-diones (**2**) and examined their antitumor activity.[8] All compounds exhibited a high degree of activity, but the 3-methoxy-4-hydroxybenzylidene derivatives possessed the greatest potency.[8] Recently, using this innovative pharmacophore, Hori and co-workers have prepared new derivatives of 2-hydroxyarylidene-4-cyclopentene-1,3-diones as new candidates for antitumor agents.[9] Their comprehensive evaluation of these agents with respect to protein tyrosine kinase (PTK) inhibition, mitochondrial inhibition, antitumor activity, and hepatotoxicity demonstrates that PTK inhibitors TX-1123 and TX-1925 (Fig. 2) are more promising

Keywords: Ferrocenylidenecyclopentenediones; Ferrocenyl quinones; Alkynylcyclobutenones; Cyclobutenediones; Cyclobutenols; Rearrangement; Radicals.
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URL: http://www.chem.metu.edu.tr/academic/zora/index.htm

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doi:10.1016/j.tet.2006.08.078

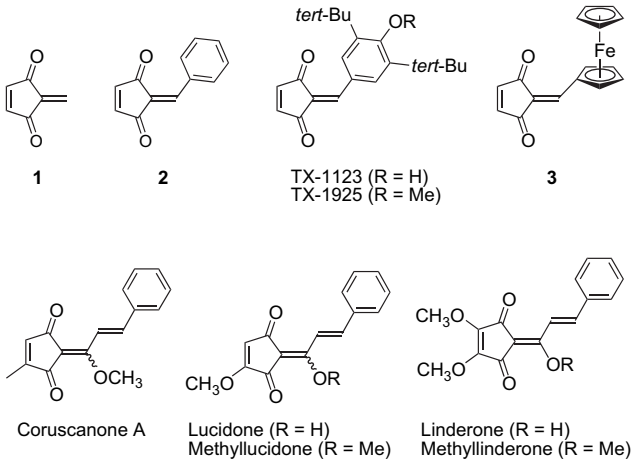


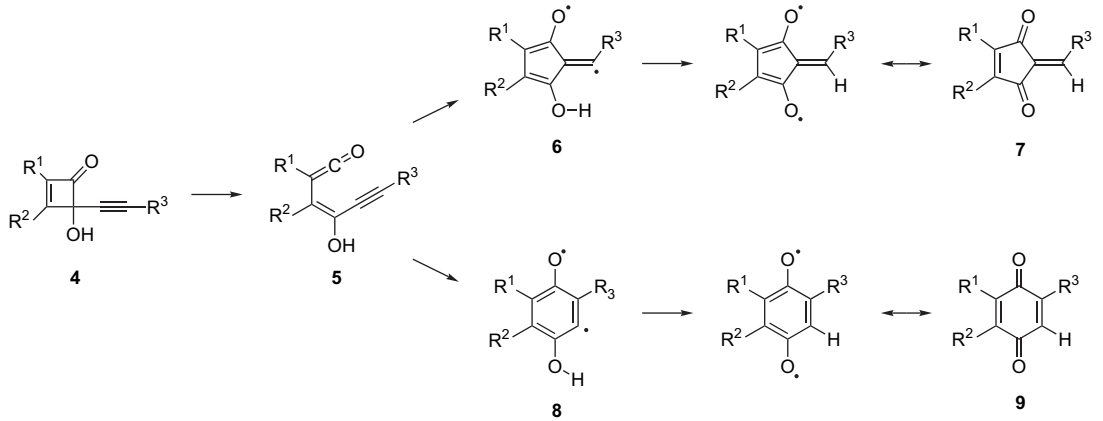
Figure 2. Structures of 2-methylene-4-cyclopentene-1,3-dione (**1**) and related pharmacophores and molecules.

candidates for antitumor agents than well known compound tyrphostin AG17.[9] Naturally occurring lucidone, linderone, and their methyl derivatives methyllucidone and methyllinderone,[10,11] and coruscanone A[12] also contain a 2-methylene-4-cyclopentene-1,3-dione (**1**) pharmacophore in their structures and show farnesyl protein transferase inhibition, antitumor, and/or antifungal activities.

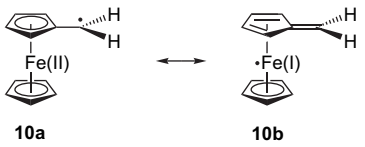
Our attention was then directed toward the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-dione derivatives, such as **3**, since the incorporation of the essential structural features of 2-methylene-4-cyclopentene-1,3-dione (**1**) pharmacophore with a ferrocenyl moiety could provide compounds with enhanced antitumor activities. Surprisingly, 2-ferrocenylidene-4-cyclopentene-1,3-diones (**3**) are not known. The development of a general synthetic entry to such compounds is therefore of considerable interest since it could lead to a new source of biologically active compounds.

Recently, as shown by Moore and co-workers,[13] 4-alkynyl-4-hydroxycyclobutenones (**4**) have emerged as valuable reagents in organic synthesis since such cyclobutenones undergo a remarkably selective electrocyclic ring opening to give the corresponding conjugated ketenes **5** (Scheme 1). Ketenes **5** then experience five- and/or six-membered ring closure to afford diradicals **6** and/or **8**, which finally lead to 2-alkylidene-4-cyclopentene-1,3-diones (**7**) and/or benzoquinones (**9**) after an intramolecular transfer of the H atom. The selectivity of the rearrangement to give either cyclopentenediones **7** or benzoquinones **9** is significantly influenced by the R^3 substituent in that radical-stabilizing groups, such as alkoxy, phenyl, and trimethylsilyl, favor exclusively, or in part, the cyclopentenedione formation.[14,15] As suggested by Moore,[13b,c] the aromatic stabilization associated with six-membered ring formation is apparently outweighed by direct stabilization of the vinyl radical by the adjacent R^3 substituent when five-membered ring formation takes place. Recently, Engels and co-workers have theoretically studied the substituent effects on the cyclization of 1,3-hexadiene-5-ynone derivatives to the corresponding five- and six-membered diradicals at the density functional theory (DFT) level (B3LYP/6-31G*).[16] They have found that, in addition to a radical-stabilizing group such as Ph as the alkyne substituent (R^3), electron donor groups such as OH and OMe at the other positions are required to make five-membered ring formation as the major pathway. The nature of certain electronic effects of a ferrocenyl substituent was studied by Nesmeyanov et al.[17] It was found that the ferrocenyl substituent exhibits a strong positive inductive effect and a weak positive conjugation effect. Recently, Creary et al. examined the quantitative ability of the ferrocenyl group to stabilize free radicals by employing the experimental methylenecyclopropane rearrangement probe.[18] They found that a ferrocenyl group is 1.6 times better at stabilizing an α radical than a phenyl group. Computational studies have also been carried out in order to gain further insight into the radical-stabilizing ability of ferrocenyl group.[19] DFT (B3LYP/LANL2DZ) calculations on ferrocenyl-substituted methyl radical **10** showed that the radical-stabilizing ability of the ferrocenyl group can be explained by a spin delocalization mechanism involving the Fe atom and a major contribution from an η^4-form, as represented by **10b** (Scheme 2), where the iron is formally a 17-electron system in the +1 oxidation state. Moreover, calculations at the same level indicated that ferrocenylmethyl radical **10** is more stable than the benzyl radical by 1.5 kcal mol^{-1}, in agreement with the experimental results.[19]

In light of these results, it is expected that the thermal rearrangement of alkynylcyclobutenones **4** bearing a ferrocenyl



Scheme 1. Mechanism for the formation of 2-alkylidenecyclopentenediones **7** and benzoquinones **9** from 4-alkynylcyclobutenones **4**.



Scheme 2. Stabilization of ferrocenylmethyl radical.

group as the R^3 substituent should produce 2-ferrocenylidene-4-cyclopentene-1,3-dione derivatives as the major product of the reaction. This methodology, however, has not been utilized for the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones, presumably due to the scarce availability of the starting ferrocenylcyclobutenones. As part of our general involvement in ferrocene-containing potential pharmaceuticals, we have investigated the synthesis of ferrocenylcyclobutenones and their rearrangements to 2-ferrocenylidene-4-cyclopentene-1,3-diones.[20] We herein report the results of this study.

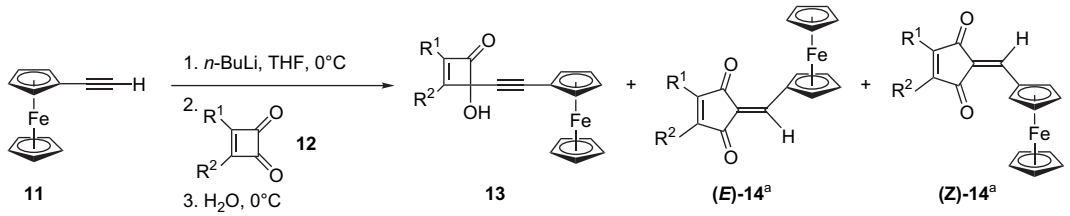
2. Results and discussion

Initially, starting materials were prepared. The synthesis of ethynylferrocene **11** was accomplished from acetylferrocene in two steps according to a well known literature procedure[21] (acetylferrocene is readily available in large quantities from ferrocene according to a standard protocol).[22] Treatment of acetylferrocene with phosphorus oxychloride in DMF led to (2-formyl-1-chlorovinyl)ferrocene, which upon base-induced elimination using aqueous sodium hydroxide in dioxane provided ethynylferrocene **11** in good yield.[21] Cyclobutenediones **12A–D** were prepared from squaric acid according to Liebeskind's procedure.[23] For the synthesis of diphenylcyclobutenedione **12E**, squaric acid was first reacted with thionyl chloride to afford semisquaric chloride.[24] Friedel–Crafts reaction of semisquaric chloride with ferrocene in the presence of $AlCl_3$ produced cyclobutenedione **12E**.[25]

We next synthesized 4-ferrocenylethynylcyclobutenones **13** as shown in Table 1. Treatment of ethynylferrocene **11** with *n*-butyllithium produced in situ lithioethynylferrocene that was further reacted with cyclobutenediones **12** to yield the corresponding cyclobutenones **13**. It should be noted that 4-ferrocenylethynyl-substituted cyclobutenones **13**, especially 2-phenyl-substituted cyclobutenones **13C** and **13E**, were found to be quite reactive and, during the isolation, they partly decomposed and/or rearranged to the corresponding 2-ferrocenylidenecyclopentenediones **14** in varying amounts. Interestingly, 2-methyl-substituted cyclobutenones **13B** and **13D** were insoluble in hexane and it was possible to obtain these compounds in pure form by filtrating their hexane solution. The easy isolation of these derivatives prevented in part their rearrangement to the corresponding cyclopentenediones, and allowed us to have their pure samples for spectroscopic identification. Notably, 2-phenyl-substituted cyclobutenones **13C** and **13E** were highly reactive since they started more rapidly to decompose and/or undergo rearrangement, and it was not possible to obtain pure samples for characterization. That is why, after synthesis, 2-phenyl-substituted cyclobutenones **13C** and **13E** were isolated as crude products and immediately subjected to rearrangement. Moreover, it was observed that, during the chromatographic purification, silica gel accelerated the conversion of cyclobutenones **13** to cyclopentenediones **14** to some extent.

Subsequently, we investigated the rearrangements of 4-ferrocenylethynylcyclobutenones **13** to 2-ferrocenylidenecyclopentenediones **14**. The results are summarized in Table 2. In fact, for these conversions, we employed three different procedures. Firstly, we used a typical thermolysis procedure, which, in general, is the most commonly used protocol for such rearrangements. For this purpose, cyclobutenones **13** were heated in refluxing dioxane at 100 °C for 4 h (Method A). Recently, to run reactions on the surface of solids has attracted considerable interest since, in this way, reactions can be accelerated or new chemistry may occur.[26] We found that when heated with silica gel as a solvent free grinded solid mixture in an oven at 125 °C for a short reaction time, such as 15 min (Method B), cyclobutenones **13** were quickly rearranged to cyclopentenediones **14**. More importantly, stirring a mixture of cyclobutenones **13** and silica gel in ethyl

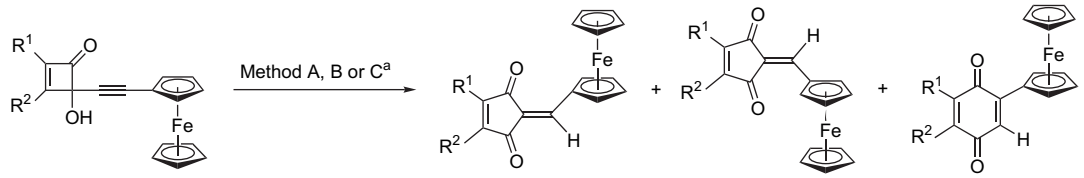
Table 1. Synthesis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**13**)



Entry	Starting compound	R^1	R^2	Products (Yields, %)[b]
1	**11A+12A**	*i*-PrO	*i*-PrO	**13A** (65)+**14A** (5)
2	**11A+12B**	Me	*i*-PrO	**13B** (34)+(*E*)-**14B** (19)+(*Z*)-**14B** (9)
3	**11A+12C**	Ph	*i*-PrO	**13C**[c]+(*E*)-**14C** (35)
4	**11A+12D**	Me	Me	**13D** (38)+**14D** (22)
5	**11A+12E**	Ph	Ph	**13E**[c]+**14E** (37)

[a] When R^1 and R^2 are the same, this structure presents compound **14**.
[b] Isolated yields.
[c] For this compound, yield calculation could not be made since, during isolation, it was continuously decomposed and/or rearranged to the corresponding cyclopentenedione. That is why this compound was isolated as a crude product and immediately subjected to rearrangement.

Table 2. Synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (**14**)



13 **(*E*)-14**[b] **(Z)-14**[b] **15**

Entry	Starting compound	R^1	R^2	Method[a]	Products (Yields, %)[c]
1	**13A**	*i*-PrO	*i*-PrO	A	**14A** (70)+**15A** (2)
2	**13A**	*i*-PrO	*i*-PrO	B	**14A** (67)
3[d]	**13A**	*i*-PrO	*i*-PrO	C	**14A** (34)
4	**13B**	Me	*i*-PrO	A	(*E*)-**14B** (61)+(*Z*)-**14B** (3)+**15B** (4)
5	**13B**	Me	*i*-PrO	B	(*E*)-**14B** (45)+(*Z*)-**14B** (32)
6	**13B**	Me	*i*-PrO	C	(*E*)-**14B** (51)+(*Z*)-**14B** (6)
7	**13C**	Ph	*i*-PrO	A	(*E*)-**14C** (53)[e]
8	**13C**	Ph	*i*-PrO	C	(*E*)-**14C** (56)[e]
9	**13D**	Me	Me	A	**14D** (55)+**15D** (8)
10	**13D**	Me	Me	B	**14D** (71)+**15D** (5)
11	**13D**	Me	Me	C	**14D** (74)+**15D** (8)
12	**13E**	Ph	Ph	A	**14E** (58)[f]
13	**13E**	Ph	Ph	C	**14E** (45)[f]

[a] Method A: dioxane, 100 °C, 4 h; Method B: SiO_2, 125 °C, 15 min; Method C: SiO_2, ethyl acetate, 25 °C, 24 h.
[b] When R^1 and R^2 are the same, this structure presents compound **14**.
[c] Isolated yields.
[d] For this reaction, reaction time was 48 h.
[e] For this compound, yield was calculated from ethynylferrocene (**11**) since, in this reaction, crude cyclobutenone **13C**, obtained from **11**, was used.
[f] For this compound, yield was calculated from ethynylferrocene (**11**) since, in this reaction, crude cyclobutenone **13E**, obtained from **11**, was used.

acetate at room temperature for overnight (Method C) also afforded cyclopentenediones **14**, which is a clear indicative of the high reactivity of 4-ferrocenylethynyl-substituted cyclobutenones **13**. To the best of our knowledge, these last two procedures (Methods B and C) have not been used previously for effecting such rearrangements. In terms of chemical yields, all methods we used appear to be comparable with each other.

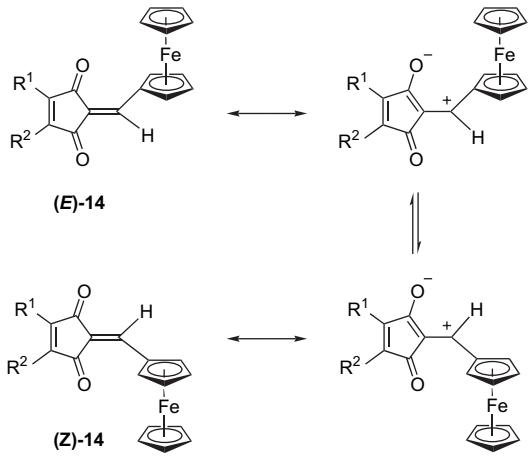
As can be seen in Table 2, all protocols produced the expected cyclopentenediones **14** as the major or single product of the reaction. From unsymmetrically substituted cyclobutenones **13B** and **13C** (Table 2, entries 4–8), mostly or exclusively *E* isomers of cyclopentenediones ((*E*)-**14**) were obtained. In reactions with **13B**, *Z* isomer ((*Z*)-**14**) was also observed but in minor amounts except the one case (Table 2, entry 5), in which *Z* isomer was the significant proportion of the product. In some cases, ferrocenyl quinones were also resulted from these reactions as the minor products.[27] On the basis of the mechanism in Scheme 1 as suggested by Moore,[13] the most or exclusive formation of 2-ferrocenylidenecyclopentenediones **14**, as compared to quinones, clearly shows the radical-stabilizing ability of the ferrocenyl group, a result consistent with the findings of Creary as well.[18,19]

As mentioned before, the reactions of Methods B and C were performed in the presence of silica gel. To verify the silica gel effect, the reactions of **13A** in entries 2 and 3 of Table 2 were repeated in the absence of silica gel. First reaction gave a very low yield of cyclopentenedione **14A**. In the second reaction, conversion to **14A** was almost insignificant. Both results clearly demonstrate that the use of silica gel in these reactions, i.e., in Methods B and C, is vital. The effect of silica gel should be similar to that of a weak Lewis and/or Brønsted acid.

It is interesting to note that 2-ferrocenylidenecyclopentenediones **14** and ferrocenyl quinones **15** can be easily differentiated from each other via their respective ^{1}H NMR spectra. The vinyl proton in quinones **15** appears at 6.67–6.80 ppm while that in cyclopentenediones **14** resonates at 7.22–7.69 ppm since the latter is conjugated to the two carbonyl groups and, as expected, it is more deshielded. In addition, during mass analysis under FAB conditions, ferrocenyl quinones **15** were reduced to the corresponding hydroquinones, as indicated by the MS and HRMS results, but such reductions were not observed for cyclopentenediones **14**. We also realized that ferrocenyl-substituted cyclopentenediones **14** and quinones **15** can be recognized by their colors since cyclopentenediones **14** are in claret red or purple color while quinones **15** are in green color.

The major or exclusive isomer of differently substituted cyclopentenediones **14B** and **14C** was assigned as the *E* isomer. As shown by Moore,[13] in the conversion of diradical intermediate **6** to alkylidenecyclopentenedione **7** (Scheme 1), the H atom migration occurs intramolecularly, which translates to the indicated *E* stereochemistry of the major or exclusive isomer of **14B** and **14C**. The formation of the minor *Z* isomer in some cases may not actually represent a new reaction pathway since it is a secondary product of the reaction and results from the initially formed *E* isomer through partial isomerization or equilibration. It was already shown that the treatment of *E* isomer of a 2-benzylidene-4-cyclopentene-1,3-dione derivative with silica gel resulted in its facile equilibration with the *Z* isomer.[13b] Similarly, when heated with silica gel as a grinded solid mixture at

125 °C for 1 h, pure (*E*)-**14B** equilibrated with its *Z* isomer. A possible mechanism for this isomerization is given in Scheme 3. During the *E*–*Z* isomerization, a positive charge develops at the exo β-carbon atom adjacent to ferrocenyl group (Scheme 3), but it is well stabilized since the ferrocenyl group is much more effective at carbocation stabilization than it is at radical stabilization.[18] In addition, the ferrocenyl group is a better carbocation stabilizing group than the phenyl group.[28]



Scheme 3. A possible mechanism for the *E*–*Z* isomerization of 2-ferrocenylidenecyclopentenediones **14**.

3. Conclusion

In summary, we have described a squarate-based synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (**14**), which are the first examples of these kind, containing a ferrocene moiety. When refluxed in dioxane at 100 °C, heated with silica gel as a solvent free grinded solid mixture at 125 °C or stirred with silica gel in ethyl acetate at room temperature, 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**13**) afford 2-ferrocenylidenecyclopentenediones **14** as the major or single product of the reaction, accompanied by minor amounts of ferrocenyl quinones in some cases. The formation of 2-ferrocenylidene-4-cyclopentene-1,3-diones is attributed to the radical-stabilizing ability of the ferrocenyl group, which has not been utilized before in such reactions.

4. Experimental

4.1. General consideration

Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). DEPT ^{13}C NMR information is given in parenthesis as C, CH, CH_2, and CH_3. Infrared spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), and vw (very weak). Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a VG-7070E magnetic sector instrument using fast atom bombardment (FAB); *m*/*z* values are reported, followed by the relative intensity in parentheses. The matrix used for FAB was ethylene glycol or a mixture of dithiothritol and dithioerithitol. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230–400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Ethynylferrocene (**11**)[21] and cyclobutenediones **12A**–**E** were synthesized according to the well known literature procedures.[23–25] All other commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF, and dioxane were distilled from sodium/benzophenone ketyl. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon.

4.2. General procedure for synthesis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (13) (Table 1)

To a solution of ethynylferrocene (**11**)[21] (252 mg, 1.2 mmol) in THF (15 mL) at 0 °C under argon was added via syringe *n*-butyllithium (0.65 mL of a 1.7 M hexane solution, 1.1 mmol) over a period of 15 min. The mixture was stirred for 45 min at the same temperature, and then transferred via cannula to a solution of the corresponding cyclobutenedione **12**[23–25] (1.0 mmol) in THF (15 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 3 h and then quenched with water (10 mL) at −78 °C. The mixture was allowed to warm to room temperature and diluted with diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with ether (2×50 mL). After drying over $MgSO_4$, the combined organic layers were removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate followed by 4:1 hexane/ethyl acetate as the eluent. The products given in Table 1 were isolated with the indicated yields.

4.3. Spectral data for cyclobutenones 13

4.3.1. 4-Ferrocenylethynyl-4-hydroxy-2,3-diisopropoxy-2-cyclobutenone (13A). R_f=0.30 in 4:1 C_6H_{14}/EtOAc; off yellow solid; 265.3 mg (65%); ^{1}H NMR ($CDCl_3$): δ 5.01 (septet, 1H, *J*=6.1 Hz), 4.87 (septet, 1H, *J*=6.1 Hz), 4.41 (s, 2H), 4.17 (s, 7H), 3.10 (br s, 1H), 1.45 (d, 3H, *J*=6.1 Hz), 1.43 (d, 3H, *J*=6.1 Hz), 1.29 (d, 3H, *J*=6.1 Hz), 1.28 (d, 3H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 181.0 (C), 164.8 (C), 134.3 (C), 88.3 (C), 80.0 (C), 79.7 (C), 78.2 (CH), 74.5 (CH), 72.0 (CH), 70.4 (CH), 69.3 (CH), 63.9 (C), 23.1 (CH_3, two methyl carbons overlap), 22.9 (CH_3, two methyl carbons overlap); IR (CH_2Cl_2): 3358 (w), 3323 (br), 2975 (m), 2928 (m), 2223 (w), 1773 (s), 1627 (vs), 1458 (w), 1388 (s), 1322 (s), 1261 (s), 1096 (s) cm^{-1}; MS (FAB): 409 ($[M+H]^+$, 55), 408 ($[M]^+$, 100), 395 (11), 324 (19), 311 (6), 213 (18), 199 (7), 137 (17), 136 (16), 43 (11), 41 (9); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1034. Found: 408.1024.

4.3.2. 4-Ferrocenylethynyl-4-hydroxy-3-isopropoxy-2-methyl-2-cyclobutenone (13B). R_f=0.25 in 4:1 C_6H_{14}/EtOAc; brownish yellow solid; 123.8 mg (34%); ^{1}H NMR ($CDCl_3$): δ 5.08 (septet, 1H, J=6.1 Hz), 4.40 (s, 2H), 4.17 (s, 7H), 3.34 (s, 1H), 1.68 (s, 3H), 1.50 (d, 3H, J=6.1 Hz), 1.46 (d, 3H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.6 (C), 180.3 (C), 124.9 (C), 89.4 (C), 84.2 (C), 79.9 (C), 78.5 (CH), 72.0 (CH), 70.4 (CH), 69.4 (CH), 63.8 (C), 23.4 (CH_3), 23.1 (CH_3), 7.0 (CH_3); IR (CH_2Cl_2): 3559 (w), 3308 (br), 2976 (w), 2926 (vw), 2223 (w), 1764 (s), 1623 (vs), 1463 (vw), 1397 (s), 1312 (s), 1097 (s) cm^{-1}; MS (FAB): 365 ([M+H]$^+$, 81), 364 ([M]$^+$, 87), 347 (82), 322 (100), 305 (25), 295 (16), 257 (96), 255 (13), 210 (11), 183 (6), 157 (8), 121 (20), 85 (9); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

4.3.3. 4-Ferrocenylethynyl-4-hydroxy-2,3-dimethyl-2-cyclobutenone (13D). R_f=0.17 in 4:1 C_6H_{14}/EtOAc; brown solid; 121.6 mg (38%); ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 2H), 4.18 (s, 2H), 4.16 (s, 5H), 2.58 (s, 1H), 2.20 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8 (C), 177.2 (C), 151.1 (C), 89.2 (C), 87.1 (C), 80.4 (C), 72.0 (CH), 70.6 (CH), 69.4 (CH), 63.9 (C), 10.9 (CH_3), 8.4 (CH_3); IR (CH_2Cl_2): 3568 (w), 3392 (br), 3099 (vw), 2960 (vw), 2219 (m), 1765 (vs), 1637 (s), 1432 (w), 1380 (w), 1303 (w), 1259 (w), 1176 (w), 1099 (m) cm^{-1}; MS (FAB): 321 ([M+H]$^+$, 68), 320 ([M]$^+$, 100), 303 (76), 275 (50), 255 (90), 253 (11), 183 (10), 155 (14), 121 (13), 115 (4), 85 (5); HRMS (FAB) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

4.4. General procedures for the synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones (14) (Table 2)

4.4.1. Method A. A dioxane (15 mL) solution of the corresponding cyclobutenone **13** (0.50 mmol) was heated to reflux at 100 °C under argon for a period of 4 h. The mixture was then allowed to cool to room temperature and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method A were isolated with the indicated yields.

4.4.2. Method B. A ground mixture of the corresponding cyclobutenone **13** (0.10 mmol) and silica gel (0.5 g) were heated on a watch glass in an oven at 125 °C for 15 min. After cooling to room temperature, the residue was loaded onto a silica gel flash column and purified by using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method B were isolated with the indicated yields.

4.4.3. Method C. A mixture of the corresponding cyclobutenone **13** (0.10 mmol) and silica gel (0.5 g) in ethyl acetate (10 mL) was stirred at room temperature under argon for 24 h (note that for the reaction in Table 2, entry 3, reaction time was 48 h). After the solvent was removed on a rotary evaporator, the residue was loaded onto a silica gel flash column and purified by using 9:1 hexane/ethyl acetate as the eluent. The products given in Table 2 according to Method C were isolated with the indicated yields.

4.5. Spectral data for cyclopentenediones 14 and ferrocenyl quinones 15

4.5.1. 2-Ferrocenylidene-4,5-diisopropoxy-4-cyclopentene-1,3-dione (14A). R_f=0.40 in 9:1 C_6H_{14}/EtOAc; claret red oily solid; 142.8 mg (70%, Method A), 27.3 mg (67%, Method B), 13.9 mg (34%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 5.50 (septet, 1H, J=6.2 Hz), 5.44 (septet, 1H, J=6.2 Hz), 5.14 (pseudo t, 2H, J=1.7 Hz), 4.56 (pseudo t, 2H, J=1.7 Hz), 4.13 (s, 5H), 1.36 (d, 6H, J=6.2 Hz), 1.34 (d, 6H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 186.1 (C), 150.9 (C), 147.1 (C), 139.0 (CH), 121.6 (C), 76.2 (C), 74.9 (CH), 74.7 (CH), 74.2 (CH), 73.4 (CH), 70.4 (CH), 23.5 (CH_3), 23.4 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1668 (vs), 1620 (vs), 1461 (vw), 1377 (m), 1305 (s), 1102 (s), 1029 (s) cm^{-1}; MS (FAB): 409 ([M+H]$^+$, 36), 408 ([M]$^+$, 75), 367 (12), 366 (9), 324 (41), 301 (27), 259 (100), 186 (9), 135 (10), 121 (8), 103 (18), 85 (18), 45 (34); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1035.

4.5.2. (*E*)-2-Ferrocenylidene-4-isopropoxy-5-methyl-4-cyclopentene-1,3-dione ((*E*)-14B). R_f=0.58 in 9:1 C_6H_{14}/EtOAc; claret red solid; mp 99.5–100.3 °C; 111.0 mg (61%, Method A), 16.4 mg (45%, Method B), 18.6 mg (51%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 5.61 (septet, 1H, J=6.1 Hz), 5.21 (s, 2H), 4.60 (s, 2H), 4.15 (s, 5H), 1.93 (s, 3H), 1.36 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 191.0 (C), 189.5 (C), 163.8 (C), 140.7 (CH), 134.7 (C), 122.6 (C), 76.1 (C), 74.5 (CH) (ferrocenyl CH and isopropoxy CH overlap), 73.8 (CH), 70.5 (CH), 23.7 (CH_3), 7.6 (CH_3); IR (CH_2Cl_2): 2980 (vw), 1712 (w), 1668 (vs), 1605 (vs), 1492 (w), 1376 (vs), 1319 (m), 1247 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 365 ([M+H]$^+$, 73), 364 ([M]$^+$, 100), 322 (35), 299 (16), 257 (100), 155 (12), 119 (26), 85 (30); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

4.5.3. (*Z*)-2-Ferrocenylidene-4-isopropoxy-5-methyl-4-cyclopentene-1,3-dione ((*Z*)-14B). R_f=0.45 in 9:1 C_6H_{14}/EtOAc; claret red solid; 5.5 mg (3%, Method A), 11.7 mg (32%, Method B), 2.2 mg (6%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 5.58 (septet, 1H, J=6.1 Hz), 5.20 (s, 2H), 4.64 (s, 2H), 4.18 (s, 5H), 1.97 (s, 3H), 1.40 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 192.3 (C), 188.0 (C), 166.3 (C), 141.0 (CH), 130.0 (C), 122.2 (C), 76.2 (C), 74.6 (CH), 74.4 (CH), 73.8 (CH), 70.5 (CH), 23.6 (CH_3), 7.5 (CH_3).

4.5.4. (*E*)-2-Ferrocenylidene-4-isopropoxy-5-phenyl-4-cyclopentene-1,3-dione ((*E*)-14C). R_f=0.48 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 130.5–131.4 °C; 112.9 mg (53%, Method A), 23.9 mg (56%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, J=7.2 Hz), 7.45–7.35 (m, 4H), 5.91 (septet, 1H, J=6.1 Hz), 5.27 (pseudo t, 2H, J=1.7 Hz), 4.65 (pseudo t, 2H, J=1.7 Hz), 4.15 (s, 5H), 1.41 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 189.6 (C), 189.4 (C), 162.7 (C), 142.3 (CH), 132.1 (C), 130.0 (CH), 129.4 (CH), 128.5 (CH), 122.7 (C), 76.1 (C), 75.7 (CH), 74.9 (CH), 74.1 (CH), 70.6 (CH), 23.8 (CH_3); IR (CH_2Cl_2): 2982 (vw), 1712 (w), 1668 (vs), 1617 (s), 1593 (m), 1491 (vw), 1376 (m), 1322 (w), 1268 (m), 1126 (w), 1088 (w), 1023 (m) cm^{-1}; MS (FAB): 427 ([M+H]$^+$, 87), 426 ([M]$^+$, 100), 384 (47), 361

(12), 320 (30), 319 (91), 245 (4), 189 (4), 149 (4), 121 (5), 85 (4); HRMS (FAB) calcd for $C_{25}H_{22}FeO_3$: 426.0918. Found: 426.0908.

4.5.5. 2-Ferrocenylidene-4,5-dimethyl-4-cyclopentene-1,3-dione (14D). R_f=0.49 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 170.5–171.6 °C; 88.0 mg (55%, Method A), 22.7 mg (71%, Method B), 23.7 mg (74%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H), 5.24 (pseudo t, 2H, J=1.7 Hz), 4.64 (pseudo t, 2H, J=1.7 Hz), 4.13 (s, 5H), 2.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 194.7 (C), 193.5 (C), 154.0 (C), 150.2 (C), 142.8 (CH), 121.1 (C), 76.0 (C), 74.6 (CH), 74.1 (CH), 70.6 (CH), 9.6 (CH_3), 9.5 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1604 (vs), 1492 (w), 1376 (vs), 1326 (s), 1248 (m), 1126 (s), 1088 (s), 1023 (s) cm^{-1}; MS (FAB): 321 ([M+H]$^+$, 51), 320 ([M]$^+$, 100), 256 (23), 255 (84), 149 (14), 121 (9), 85 (9), 69 (6); HRMS (FAB) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0514.

4.5.6. 2-Ferrocenylidene-4,5-diphenyl-4-cyclopentene-1,3-dione (14E). R_f=0.42 in 4:1 C_6H_{14}/EtOAc; purple solid; mp 198.3–199.2 °C; 129.1 mg (58%, Method A), 20.0 mg (45%, Method C); ^{1}H NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.46–7.40 (m, 4H), 7.38–7.31 (m, 6H), 5.34 (s, 2H), 4.72 (s, 2H), 4.21 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 193.2 (C), 192.0 (C), 151.0 (C), 147.5 (C), 146.2 (CH), 130.6 (CH), 130.5 (CH), 130.3 (C), 130.1 (C), 130.0 (CH), 129.5 (C), 128.8 (CH), 76.2 (C), 75.1 (CH), 74.8 (CH), 70.8 (CH), note that CH peaks of phenyl groups overlap; IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1616 (vs), 1606 (vs), 1492 (w), 1376 (vs), 1326 (m), 1248 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 446 ([M+2H]$^+$, 39), 445 ([M+H]$^+$, 100), 444 ([M]$^+$, 81), 379 (67), 377 (9), 323 (6), 279 (5), 202 (5), 135 (8), 119 (15), 85 (13); HRMS (FAB, [M]$^+$) calcd for $C_{28}H_{20}FeO_2$: 444.0813. Found: 444.0825; HRMS (FAB, [M+H]$^+$) calcd for $C_{28}H_{21}FeO_2$: 445.0891. Found: 445.0914.

4.5.7. 5-Ferrocenyl-2,3-diisopropoxy-1,4-benzoquinone (15A). R_f=0.41 in 9:1 C_6H_{14}/EtOAc; green solid; 4.1 mg (2%, Method A); ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.91 (s, 2H), 4.89 (septet, 1H, J=6.2 Hz), 4.74 (septet, 1H, J=6.2 Hz), 4.57 (s, 2H), 4.13 (s, 5H), 1.33 (d, 6H, J=6.2 Hz), 1.31 (d, 6H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 184.8 (C), 184.0 (C), 147.2 (C), 145.8 (C, two quaternary carbons overlap), 125.5 (CH), 76.3 (C), 76.2 (CH, two isopropoxy CH overlap), 72.5 (CH), 70.9 (CH), 70.1 (CH), 23.1 (CH_3), 23.0 (CH_3); IR (CH_2Cl_2): 2975 (w), 2928 (vw), 1637 (s), 1567 (s), 1453 (w), 1378 (w), 1261 (vs), 1181 (m), 1101 (s), 1049 (w) cm^{-1}; MS (FAB): 410 ([M+2H]$^+$, 100), 409 ([M+H]$^+$, 14), 408 ([M]$^+$, 16), 368 (18), 325 (23), 291 (29), 259 (24), 213 (17), 186 (8), 121 (8); HRMS (FAB) calcd for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1015.

For *5-ferrocenyl-2-isopropoxy-3-methyl-1,4-hydroquinone* (formed by reduction of **15A** during mass analysis), HRMS (FAB) calcd for $C_{22}H_{26}FeO_4$: 410.1180. Found: 410.1199.

4.5.8. 5-Ferrocenyl-2-isopropoxy-3-methyl-1,4-benzoquinone (15B). R_f=0.59 in 9:1 C_6H_{14}/EtOAc; green solid; 7.3 mg (4%, Method A); ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.92 (s, 2H), 4.91 (septet, 1H, J=6.1 Hz), 4.58 (s, 2H), 4.12 (s, 5H), 1.96 (s, 3H), 1.31 (d, 6H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 183.5 (C), 154.8 (C), 148.8 (C), 131.0 (C), 126.0 (CH), 76.6 (C), 76.3 (CH), 72.5 (CH), 70.9 (CH), 70.3 (CH), 23.4 (CH_3), 9.9 (CH_3); IR (CH_2Cl_2): 2975 (vw), 2928 (vw), 1646 (vs), 1580 (vs), 1453 (vw), 1378 (w), 1317 (vw), 1256 (s), 1181 (vs), 1096 (s), 1016 (m) cm^{-1}; MS (FAB): 366 ([M+2H]$^+$, 75), 365 ([M+H]$^+$, 68), 364 ([M]$^+$, 100), 323 (27), 322 (19), 257 (45), 229 (9), 186 (3), 149 (6), 121 (6), 85 (4); HRMS (FAB) calcd for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

For *5-ferrocenyl-2-isopropoxy-3-methyl-1,4-hydroquinone* (formed by reduction of **15B** during mass analysis), HRMS (FAB) calcd for $C_{20}H_{22}FeO_3$: 366.0918. Found: 366.0912.

4.5.9. 5-Ferrocenyl-2,3-dimethyl-1,4-benzoquinone (15D). R_f=0.53 in 9:1 C_6H_{14}/EtOAc; green solid; 12.8 mg (8% yield, Method A), 1.6 mg (5%, Method B), 2.6 mg (8%, Method C); ^{1}H NMR ($CDCl_3$): δ 6.80 (s, 1H), 4.91 (s, 2H), 4.55 (s, 2H), 4.11 (s, 5H), 1.94 (s, 3H), 1.93 (s, 3H); IR (CH_2Cl_2): 3680 (w), 3586 (vw), 2919 (w), 1641 (vs), 1623 (s), 1585 (s), 1453 (w), 1378 (w), 1317 (m), 1247 (s), 1030 (m) cm^{-1}; MS (FAB): 322 ([M+2H]$^+$, 72), 321 ([M+H]$^+$, 88), 320 ([M]$^+$, 100), 287 (5), 255 (42), 253 (4), 209 (4), 177 (4), 155 (14), 119 (24), 85 (23); HRMS (FAB, [M]$^+$) calcd for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

For *5-ferrocenyl-2,3-dimethyl-1,4-hydroquinone* (formed by reduction of **15D** during mass analysis), HRMS (FAB) calcd for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0667.

Acknowledgements

The authors would like to thank the Scientific and Technical Research Council of Turkey (104T202) and the Research Board of Middle East Technical University (BAP-2005-01-03-04) for financial support of this research, and Noel Whittaker (University of Maryland) for obtaining MS and HRMS spectra.

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