Synthesis and structural analysis of a novel iodinated cyclopentadienone *via* ring-contraction iodination and its application in synthesis of alkyne-functionalized cyclopentadienones†

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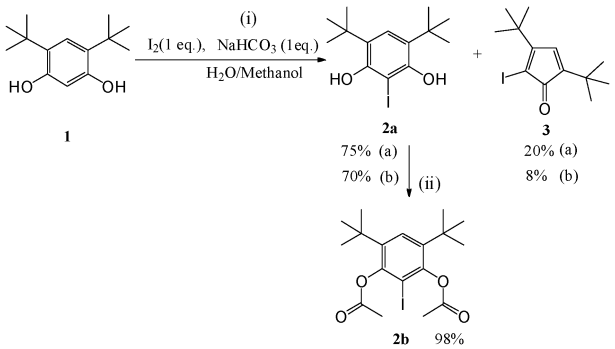
The first iodinated cyclopentadienone was isolated and its structure was confirmed by single crystal X-ray analysis. Based on this intermediate, the first direct C–C bond formation on cyclopentadienone ring was achieved. The photo induced intramolecular charge transfer of alkynylated cyclopentadienones was evaluated by solvent polarity effect on their electronic absorption spectra.

Cyclopentadienone derivatives are uniquely valuable intermediate compounds. For example, their 4 + 2 Diels–Alder reaction products with dienophiles are difficult to obtain *via* any other synthetic route.[1] They are also key precursors for the synthesis of substituted cyclobutadienes and tetrahedranes.[2] In addition they are important intermediates for various pharmaceuticals.[3] Due to their low LUMO–HOMO gap of about 1.6 eV, cyclopentadienone-containing conjugated systems exhibit unique electrical and optical properties.[4] In this study, our effort was to explore the synthetic methodology of creating cyclopentadienone-containing conjugated systems having sp–sp^2 linkages.

Cyclopentadienone itself, however, is very elusive due to its extremely high reactivity and fast dimerization rate.[5] For this reason, cyclopentadienone derivatives are normally generated *in situ* and consumed immediately in most reactions.[6] As a result, very little is known about the structures of its derivatives, and no direct C–C bond formation on the cyclopentadienone ring other than 4 + 2 cycloaddition has ever been reported. In contrast to this, we have prepared a useful cyclopentadienone derivative that is stable enough to be isolated, characterized and stored under convenient conditions. The method we have used involves a ring-contraction process.

A ring contraction reaction of 4-aryl-2,6-di-*tert*-butylphenol has been reported[7] to form various cyclopentadienones in the presence of oxygen under basic conditions. However this procedure cannot be applied in our study, where iodine substitution is essential to extend the conjugation of the cyclopentadienone ring by further alkylynation. Therefore we employed a one-pot iodination ring-contraction reaction



Scheme 1 *Reaction conditions*: (i) (a) Oxygen-free conditions, (b) in the presence of oxygen, (ii) 2.05 equiv. AcCl, 4 equiv. Et_3N, THF, − 20 °C, 30 min.

of 4,6-di-*tert*-butylresorcinol (**1**) (Scheme 1). The merit of this reaction is that the product not only possesses a cyclodienone structure but also has an iodine atom attached to its five membered ring. The carbon–iodine bond is known to be the weakest carbon–halogen bond, so that iodinated cyclopentadienone derivatives are predicted to be among the most reactive halogenated cyclopentadienones. To date no iodine-substituted cyclopentadienone has ever been reported.

Prior to this research, the only synthesis of alkyne-functionalized cyclopentadienone-like compounds was achieved by the reaction of its diacetal form,[8] and no direct alkynylation of cyclopentadienone has been reported. In this study, we report the first synthesis and structural analysis of iodine-substituted cyclopentadienone and its further reaction with terminal alkynes.

A hydroperoxylation mechanism for the formation of cyclopentadienone derivatives from the corresponding phenols was discovered by Nishinaga and Rieker which was evidenced by the discovery of epoxide intermediate formed by bubbling oxygen gas through the reaction mixture.[8] In the present study however, the yield of iodinated cyclopentadienone **3** is much higher under oxygen-free conditions (~20%) than in the presence of oxygen (8%), so that the formation of epoxide intermediate can be excluded. A possible alternative mechanism for the ring-contraction iodination reaction is shown in Scheme 2. This reaction begins with normal electrophilic aromatic substitution to give intermediate (**i**), most of which (~75%) retains its aromaticity by ejecting a proton to yield the major product 4,6-di-*tert*-butyl-2-iodobenzene-1,3-diol (**2a**). However further iodination also takes place on the 2 and 4 positions of the remaining intermediate (**i**) to give

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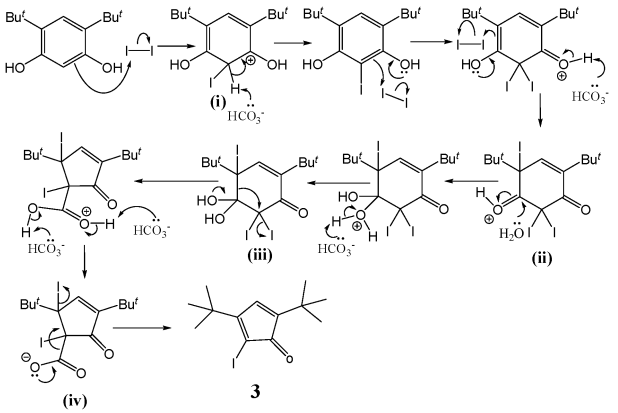
† Electronic supplementary information (ESI) available: General experimental details, NMR spectra, MS spectrum. CCDC 783904 (**2b**) and 783905 (**3**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc02543g



Scheme 2 Possible mechanism for ring-contraction iodination reaction.

the triiodocyclohexenedione intermediate (**ii**), followed by hydration of one of its ketone to give intermediate (**iii**). The ring contraction takes place by 1,2 carbon shift resulting in the elimination of one iodide on 2 position of intermediate (**iii**), followed by deprotonation to give intermediate (**iv**). Final product **3** was formed by simultaneous elimination of carbon dioxide and iodide of intermediate (**iv**).

After purification of the reaction mixture, two different compounds (**2a** and **3**) were obtained. ^{1}H NMR and ^{13}C NMR are consistent with its structure and further confirmative evidence is obtained by X-ray structural analysis. For comparison, structures of both **2b** and minor product **3** were analyzed by single crystal X-ray diffraction. The unusual bond angles for C3–C4–C5 of **3** and C1–C2–C3 of **2b** are presumably caused by the inward squeezing of the *tert*-butyl on C(4) of **3** and C(2) of **2b**, which is similar to the compression of a leaf spring (Fig. 1). Specifically, the C3–C4–C5 bond angle of **3** is 113° in comparison to 108° for all five bond angles of the five membered ring of tetracyclones,[9] and the C1–C2–C3 bond angle of **2b** is 125°.

Remarkably, in the crystal lattice of **3** there are no short contacts. This indicates that the spatial exclusion of each individual molecule dominates packing forces. In comparison, the short contact between the C=O oxygen and a hydrogen on the *tert*-butyl group influences crystal packing of **2b** (Fig. S1, ESI†).

The cross-coupling reactions of **3** with terminal alkynes were carried out under oxygen-free Sonogashira reaction conditions

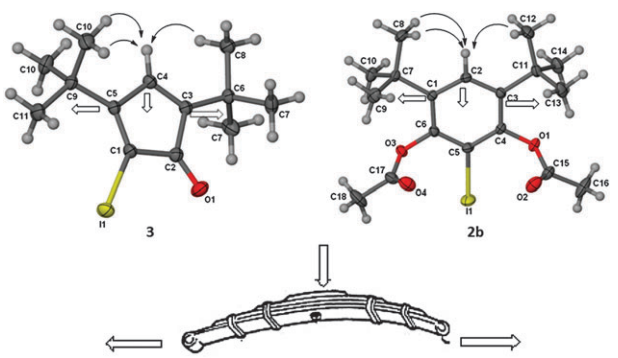
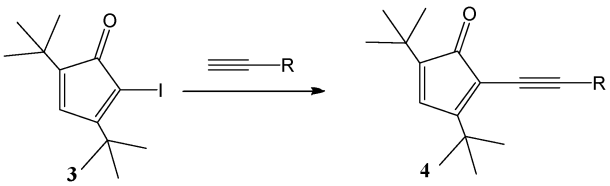


Fig. 1 Increase in bond angle for both C3–C4–C5 of **3** and C1–C2–C3 of **2b** is similar to the compression a leaf spring.



Scheme 3 *Reagents and conditions*: $Pd(PPh_3)_2Cl_2$ (0.5 mol%) CuI (1 mol%), Et_3N 10 equiv., THF, room temperature, oxygen-free conditions, 3 days, 80–97%.

Table 1 The Sonogashira cross coupling reactions of **3** with terminal alkynes

Entry	R	Yield (%)
4a	TMS	95
4b	*n*-Butyl	90
4c	*tert*-Butyl	92
4d	Cyclohexanyl	85
4e	Cyclopentylmethyl	84
4f	Cyclopropanyl	87
4g	Phenyl	97
4h	6-Methoxynaphthalen-2-yl	95
4i	Phenanthren-9-yl	94
4j	*N*,*N*-Dimethylanlin-4-yl	91
4k	3,5-Di-*tert*-butyl-4-methoxyphenyl	92
4l	*o*-Tolyl	98
4m	Ferrocenyl	91
4n	Pyridin-2-yl	[a]
4o	Thiophen-2-yl	[a]
4p	Hydroxy(phenyl)methyl	[a]
4q	2-Hydroxyethyl	[a]
4r	2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethyl	[a]
4s	3-Hydroxypropyl	80
4t	Acetyl	[a]
4u	Methylacetoxy	[a]

[a] A mixture of inseparable oligomers or polymers instead of the cross-coupling product was obtained.

(Scheme 3), which we have reported previously.[10] Both reaction yields (Table 1) and purities of products (see ESI†) are high for most alkyl-substituted and aryl-substituted terminal alkynes. For terminal alkynes with strong electron withdrawing groups (EWG) or thiophene or pyridine substituents, however, this reaction renders a mixture of inseparable various oligomers or polymers possibly *via* 4 + 2 cyclo-addition (Table 1). Interestingly, the reaction yield for the cross-coupling of **3** and 3-hydroxypropylacetylene is 80%; however, the reaction of **3** with both hydroxy(phenyl)methylacetylene and 2-hydroxyethylacetylene gives mixtures of inseparable oligomers or polymers. This indicates that for ether- or alcohol-functionalized terminal acetylenes, at least a three-methylene spacer from the oxygen atom to acetylene is required for this reaction to yield the desired cross-coupling product.

Further investigations of reactions of these EWG substituted alkynes with **3** were conducted under catalyst free conditions; no reactions occurred. This indicates that the copper and palladium catalyst are essential in assisting the 4 + 2 cyclo-addition reaction of terminal alkynes bearing EWG groups with **3** or its alkynylated products.

The electronic absorption spectra of alkynylated cyclopentadienones (λ_{max} = 460–522 nm) exhibit bathochromic shifts in comparison to unalkynylated compound **3** (λ_{max} = 448 nm), and

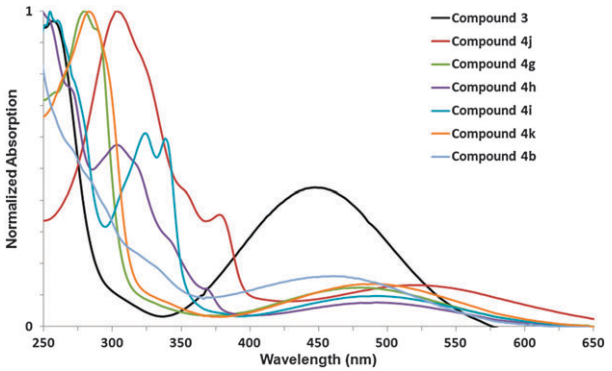


Fig. 2 Electronic absorption spectra of substituted cyclopentadieneones in chloroform. The spectrum of each compound is normalized to its main absorption maximum.

greater bathochromic shifts are observed in aromatic-substituted ethynyl cyclopentadienone (Fig. 2). Due to the sigma-aromaticity of its cyclopropanyl substituent, compound **4f** also exhibits greater bathochromic shifts (λ_{max} = 480 nm) than other alkyl substituted ethynyl cyclopentadienones. Fine tuning of absorption maxima was achieved by changing the substituent groups. For example, compound **4j** has the longest absorption-maximum wavelength, at 522 nm, due to the high electron density on its electron-donating *N*,*N*-dimethylanilin-4-yl group.

The spectral characteristics of the cyclopentadienones are presented in Table S2 (ESI†). Generally the R band (n → π* transition) of most enones are weak and poorly defined (ε_{max} < 100),[11] however all ethynyl cyclopentadienones exhibit moderate absorption in that their extinction coefficients are comparable to that of the benzenoid B-band. Notably, the R band extinction coefficients of aryl-substituted ethynyl cyclopentadienones are much higher than their alkyl-substituted counterparts. This conjugation enhanced R band absorption can be possibly explained by their resonance stabilized photoinduced intramolecular charge transfer/charge separation excited states.

Consequently, solvatochromism study of these family of compounds became essential to probe solvent polarity effect on stabilization of their ground states and possible charge transfer/separation excited states as opposed to resonance stabilization discussed above. Normally since dipole–dipole interaction and H-bonding lower the ground state energy of n orbital of carbonyl group, solvatochromic hypsochromic shifts of R band were observed in aldehydes, ketones and other carbonyl compounds.[11,12] However an opposite trend was observed in our study of solvent polarity effect on ethynyl cyclopentadieneones. Electronic absorption spectra of **3**, **4e**, **4s**, **4h**, **4j** and **4l** in seven solvents with different polarities were measured. The R-band absorption maxima of all substituted cyclopentadienones exhibit bathochromic shift with the increase of solvent polarities (Fig. S2, ESI†) in both non-halogenated solvents and chlorinated solvents. This divergence can be attributed to the fact that the energy of their charge separation/transfer excited states were lowered more by solvent polarity effect than that of ground state energy of the n orbital of their carbonyl groups. As a result, the alkyl-substituted ethynyl cyclopentadienones 4s and 4e appeared to be influenced more by solvent polarity and thus exhibit the more bathochromic shift in polar solvent in contrast to their aryl-substituted counterpart. In addition, the polarity of chlorinated solvents has more influence on $\Delta\lambda_{max}$ of substituted cyclopentadienones than non-halogenated solvents.

The authors thank a referee for suggesting a more reasonable mechanism in Scheme 2.

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