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Preparation and Photochemical Rearrangements of 2-Phenyl-2,5-cyclohexadien-1-ones. An Efficient Route to Highly Substituted Phenols

Zihong Guo* and Arthur G. Schultz†

Rensselaer Polytechnic Institute, Troy, New York 12180-3590
guo@3dp.com

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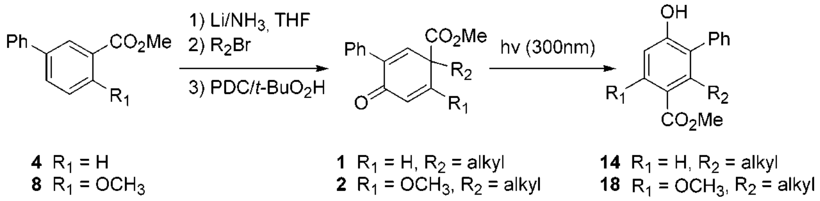
ABSTRACT



The synthesis of 2-phenyl-2,5-cyclohexadien-1-ones 1a–c and 2a–b from methyl 3-phenylbenzoate 4 and methyl 2-methoxy-5-phenylbenzoate 8 by the Birch reduction alkylation methodology is described. 1a–c and 2a–b undergo regiospecific photorearrangements at 300 nm to give tetrasubstituted phenols 14a–c and pentasubstituted phenols 18a–b, respectively. The type A photoproducts 17a–b resulting from irradiation of 2a–b at 366 nm have been isolated as ∼1:1 diastereomer mixtures. When an optimized condition is applied, a single diastereomer of 17a is obtained.

Substituted phenols are of great importance in both biosynthetic transformation and as building blocks in organic synthesis. Among the many transformations known, photochemical, acid-catalyzed, and base-catalyzed dienone−phenol rearrangements[1−3] are important methods, especially for the preparation of highly substituted phenolic substrates that are not readily available by conventional aromatic substitution chemistry. In this Letter we report the preparation of phenyl-substituted 2,5-cyclohexadien-1-ones **1** and **2** (Figure 1) by the Birch reduction−alkylation method and the photochemistry of these substrates, which leads to the formation of tetra- and pentasubstituted phenols.

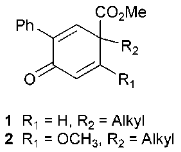


Figure 1.

The syntheses of 4,4-disubstiuted-2-phenyl-2,5-cyclohexadien-1-ones **1a−c** are outlined in Scheme 1. Methyl 3-phenylbenzoate **4** was prepared in 90% yield from methyl

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* Address correspondence to this author: 3-Dimensional Pharmaceuticals, Inc., Eagleview Corporate Center, 665 Stockton Drive, Suite 104, Exton, PA 19341.

† Deceased January 20, 2000.

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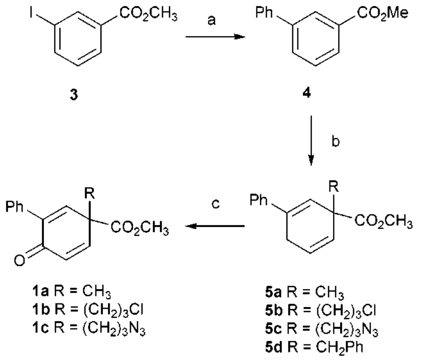
Scheme 1[a]



[a] Reagents and conditions: (a) $PhB(OH)_2$, $(Ph_3P)_4Pd$, K_2CO_3 H_2O, Tol., MeOH, reflux; (b) Li/NH_3/THF/*t*-BuOH, RBr; (c) PDC, *t*-BuO_2H, PhH, Celite.

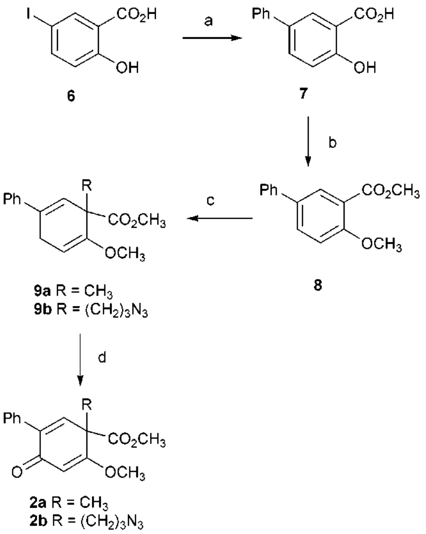
3-iodobenzoate **3** by means of Suzuki coupling with phenyl boronic acid.

Synthetic applications of the asymmetric Birch reductive alkylation of chiral nonracemic benzoic acid derivatives have been reviewed recently.[4] Although several examples of Birch reduction of biaryl compounds had been described previously, the first report of Birch reductive alkylation of biphenyl carboxylic acid derivatives appeared in 1988.[5] It is known that 2-phenylbenzoic acid derivatives provide in 40−86% yields with high stereoselectivity (>10:1) products where two of the three double bonds on the benzene ring are saturated (such as **12** and **13** in Scheme 3).[5,6] To our knowledge, Birch reductive alkylation of 3-phenyl-substituted benzoate has not been previously reported. Birch reduction of 3-phenylbenzoate **4** with lithium in NH_3−THF in the presence of 1 equiv of *tert*-butyl alcohol at −78 °C followed by addition of piperylene to consume excess metal and methylation with methyl iodide gave 3-methylated 1,4-cyclohexadiene **5a** in 88% yield (Scheme 1). It is crucial to use 2.5 equiv of lithium for the reduction step with these biaryl substrates. Under this condition, no tetrahydrobenzoate products such as **12** and **13** are isolated. The use of more than this amount results in production of the corresponding tetrahydrobenzoate products, while using less leads to the recovery of substantial amounts of the starting material. Alkylation of the resulting enolate intermediate generated by Birch reduction of **4** is also successful with other reagents. Indeed, electrophiles with functionalities such as 3-chloropropyl iodide and 3-azidopropyl iodide[7] as well as benzyl bromide were used to prepare diene products **5b**−**d** in 83−91% yields (Scheme 1). The chloro and azido substituents in the reagents remained unaffected under the reaction conditions.

Bis-allylic oxidation of **5** with *t*-BuO_2H and a catalytic amount of pyridinium dichromate provides dienones **1** in 50−70% yields (Scheme 1). An exception is **5d**, from which biphenyl **4** was isolated in 70% isolated yield upon treatment with the same allylic oxidation conditions.

The syntheses of 4,4-disubstiuted-5-methoxy-2-phenyl-2,5-cyclohexadien-1-ones **2a**−**b** are achieved by using similar procedures starting with 5-bromo- or 5-iodosalicylic acid **6** (Scheme 2). An alternative approach to preparing biaryl ester **8** in equivalent overall yields was also successful by carrying out esterification of **6** first followed by the cross aryl coupling reaction. **2a**−**b** were prepared in ∼46% overall yield in four steps.

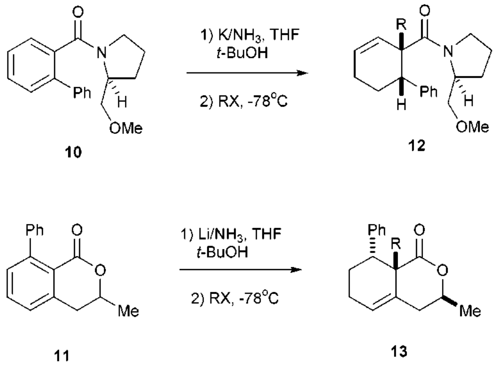
Scheme 2[a]



[a] Reagents and conditions: (a) $PhB(OH)_2$, $(Ph_3P)_4Pd$, K_2CO_3 H_2O, Tol., MeOH, reflux; (b) Me_3SO_4/K_2CO_3, acetone, reflux; (c) Li/NH_3/THF/*t*-BuOH, RBr; (d) PDC, *t*-BuO_2H, PhH, Celite.

Irradiation of a solution of **1a** in benzene through uranium glass (366 nm) provided phenol product **14a** in 87% isolated

Scheme 3



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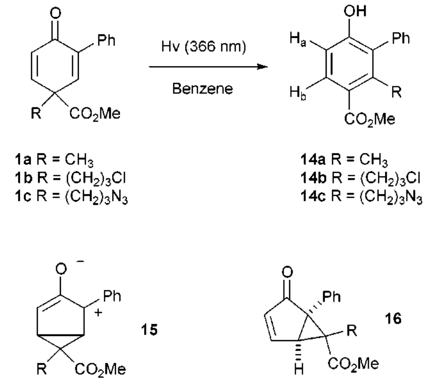
(7) 3-Azidopropyl iodides was prepared in three steps by using a known procedure, see: Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.

Scheme 4

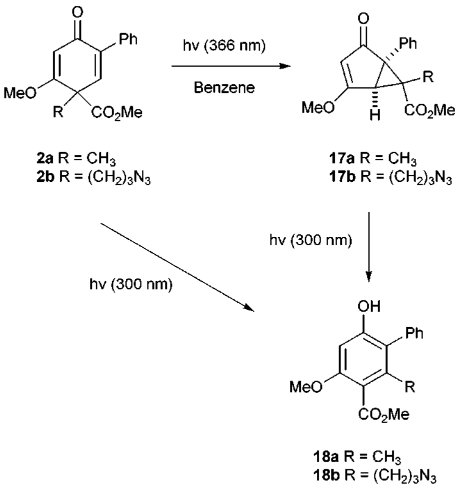


yield (Scheme 4). The photoproduct is produced by way of the type A rearrangement[8] involving oxyllyl zwitterion **15** (R = Me) giving diastereomers of unstable bicycle **16** (R = Me) (Scheme 4). Further photorearrangement of **16** under the irradiation condition gave phenol **14a**. However, in the present case none of **16** was detected nor were other products isolated from the photoreaction mixture.

The assignment of structure **14a** to the phenol resulting from photorearrangement of **1a** is based on ^{1}H NMR spectral data.[1] The photoproduct shows doublets at δ 6.87 (H_a, J = 8.7 Hz) and δ 7.28 (H_b, J = 8.7 Hz), eliminating from further consideration all possible structures in which aromatic protons would appear as singlets. **16** should be the major, if not exclusive, intermediate regioisomer, which leads to the formation of the phenol.[1] Furthermore, phenols resulting from methyl rather than carbomethoxy group migration in **16** in the photochemical reaction process were considered improbable on the basis of mechanistic expectations.[9] The effect of the 2-phenyl substituent in **1a** on the regioselectivity and yield for photochemical rearrangement of **1a** to **14a** is seen by comparison to reaction of the corresponding 3-trimethylsilyl substrate which gave a complicated mixture of three phenol products in a ratio of 1:2:4 in low yield.[10] Previously we observed that the 2-carbomethoxy and 2-cyano substituents (electron-withdrawing) provide phenols in good yields with high regioselectivity, while 2-methoxy- and 2-methyl-substituted (electron-releasing) substrates give phenols in low yields.[1]

Similarly, 2,5-cyclohexadien-1-ones **1b** and **1c** rearranged on irradiation (366 nm) to give phenols **14b** and **14c** in 75–82% isolated yields. For these two substrates, the corresponding bicyclic intermediates **16** were not observed by ^{1}H NMR spectra of the photoreaction solution, even when irradiated for a very short time (15–30 min).

Scheme 5



The photochemistry of 2-phenyl-5-methoxy-2,5-cyclohexadien-1-ones **2a–b** in degassed benzene solution is outlined in Scheme 5. In contrast to the photochemistry of the 2-phenyl analogues **1a–c**, which directly gave phenol products **14a–c** in good yields under similar conditions, irradiation of the 2-phenyl-5-methoxy substrates **2a–b** through uranium glass for 6 h provides roughly 1:1 mixtures of two diastereomers of the corresponding bicyclic intermediates **17a–b**. The yields of the ~1:1 diastereomer mixtures were indicated to be greater than 90% by inspection of product mixtures immediately after photolysis in either C_6D_6 or $CDCl_3$ solution by ^{1}H NMR spectroscopy. There was no evidence for the formation of the other regioisomers during irradiation of **2a–b** at 366 nm. It is also noteworthy that unlike the 2,5-dimethoxy and 2,6-dimethyl analogues, the azido substituent in **1c** and **2b** did not participate in the intramolecular cycloaddition process.[11]

Continued irradiation of the ~1:1 mixtures of **17a–b** at 366 nm resulted in an observable change in the diastereomer ratio. Other workers have found that 6,6-diaryl- and 6,6-dialkyl-substituted bicyclohexenone epimers do not photointerconvert under a variety of photochemical conditions.[12] However, 6-alkyl-6-carbomethoxy-4-methoxycyclohexadienones, initially obtained from photolysis of the corresponding cyclohexadienones at 366 nm as 1:1 mixtures, were found to undergo photoequilibration to ~9:1 mixtures favoring the *endo*-carbomethoxy epimer.[9a] In fact, the ratio of the mixtures from **2b** shifts to 2:1 from 1:1 upon photolysis at 366 nm for a longer time (21 h), while a more remarkable change is observed for **2a**. Irradiation of **2a** at 366 in benzene for 17 h gives **17a** as a single diastereomer along with a trace amount (<5%) of the phenol product **18a** (Scheme 5).

Unlike the 2-carbomethoxy, methoxy, cyano, and methyl analogues, which undergo rearrangement to phenols under acidic conditions,[1] **17a–b** are not sensitive to acidic conditions (CF_3CO_2H). However, irradiation through Pyrex glass (>300 nm) results in the type B photorearrangement[13] to

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give phenols **18a−b**, respectively, in good yields. Irradiation of the dienones **2a−b** at shorter wavelength (>300 nm) under the same conditions for 5 h gives **18a−b** without isolation of the bicyclic intermediates **17a−b**. The structures of **17a−b** were deduced by inspection of their spectroscopic data (IR, ^{1}H and ^{13}C NMR)[9] and by comparison with those of known compounds that have similar structures.[14]

There are several unique features of the photochemistry outlined in Scheme 4 and Scheme 5. First, the regiospecificity for the formation of the bicyclohexenones **17a−b** and phenols **14a−c** as well as **18a−b** should be a result of the presence of a 2-phenyl substituent in the molecules since it is known that the 3-methoxy group does not direct such specificity. An advantage of conversion of **2a** to **17a** by irradiation at 366 nm is that one single diastereomer can be obtained in good yield. It is obvious that the methoxy groups in **2a−b** play critical roles for stabilizing the type A photorearrangement products **17a−b** compared to **1a−c** which do not contain such a group in the molecules.

The work described in this Letter indicates that the 2-phenyl substituent in the dienone substrates **1** and **2** has a different effect on the photochemical rearrangement process as compared to those for 2-methoxy, 2-methyl, 2-carbomethoxy, and 2-cyano. The reaction sequence, including the Birch reduction alkylation and photoreaction, constitutes an efficient route to synthesis of highly substituted phenols.

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Supporting Information Available: Experimental procedures and analytical data for dienones **1** and **2**, dienes **5** and **9**, phenols **14** and **18**, and bicyclic intermediates **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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