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Appending aromatic moieties at the *para*- and *meta*-position of calixarene phenol rings via *p*-bromodienone route

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ABSTRACT

The silver-mediated nucleophilic substitution on calixarene *p*-bromodienone derivatives (the '*p*-bromodienone route') with activated aromatic substrates allows the introduction of aromatic moieties at the *para*- or *meta*-position of calixarene aromatic rings. Less reactive substrates mainly afford C–O *para*-coupled derivatives, while more activated ones mainly give inherently chiral, C–C *meta*-coupled products through a dienone–phenol rearrangement of the intermediate dienone derivative. Examples of C–C *para*-coupling and O–C coupling at the *endo* calixarene oxygen atom were also observed.

The introduction of functional moieties at the *para*-position of calixarene[1] aromatic rings (the so-called *upper*, *wide* or *exo*-rim)[2] is a general and useful approach for the synthesis of a variety of calixarene hosts of great interest in supramolecular chemistry.[1f,3] Therefore, over the past two decades several strategies to introduce new functionalities at the calixarene *exo*-rim have been developed, which include a range of electrophilic aromatic substitutions,[4] and the classical 'Claisen rearrangement route',[5] '*p*-quinone-methide route',[6] and '*p*-chloromethylation route'.[7]

In a different way from all these instances, where no direct attachment of a nucleophile to the *para* aromatic carbon can be obtained, very recently, our group has introduced the '*p*-bromodienone route'[8] as a novel approach to functionalize calixarene *exo*-rim with nucleophiles using calixarene *p*-bromodienone derivatives (exemplified by **1** in Scheme 1). At the same time, Varma and co-workers reported a related procedure in which alkoxy groups are introduced into calixarene *exo*-rim starting from calixarene spirodienone derivatives.[9] In the previous paper we reported that easily accessible calixarene *p*-bromodienone derivatives **1** undergo a silver-mediated nucleophilic substitution and a subsequent re-aromatization with a range of different *O*-nucleophiles (alcohols and carboxylates) to give *p*-alkoxy- or *p*-acyloxy-calixarenes in workable yields.[8] It was also demonstrated that the reaction can be performed directly on the *exo*/*endo* mixture of **1** because the complication of *exo*/*endo* stereoisomerism was overcome in the re-aromatization step. It was also anticipated that in order to expand the potentiality of *p*-bromodienone route other nucleophiles should be tested. Therefore, we decided to investigate the use of activated aromatic rings as nucleophiles[10] and here we wish to report on the results of this study.

In the mechanism proposed for the *p*-bromodienone route an aryloxenium cation **I** (Scheme 1),[11] is initially formed upon precipitation of AgBr, which can be captured by the present *O*-nucleophiles (alcohols and carboxylates).[8] Therefore, it can be expected that this cation could be intercepted by sufficiently activated aromatic substrates by means of an electrophilic aromatic substitution. Resorcinol **2a** was initially chosen as nucleophile due to its high reactivity toward electrophilic aromatic substitution. The mixture of *exo*/*endo* stereoisomers of **1**, obtained directly by oxidation of tripropoxy-*p*-*tert*-butylcalix[4]arene with trimethylphenylammonium tribromide,[12] was treated with a cold solution of $AgClO_4$ and resorcinol **2a** (Scheme 1) in DME for 2 h at 0 °C in the presence of Na_2CO_3 as a base.[13] Column chromatography on silica gel of the reaction mixture afforded derivatives **3a** and **4a** in 10% and 30% yield, respectively (Table 1, entry 'a').[13,14]

The structure of **3a** was easily assigned by means of spectral analysis. In particular, the presence of a pseudomolecular ion peak at *m*/*z* 827 in the ESI(+) mass spectrum confirmed the molecular formula. The C_s symmetry was confirmed by pertinent signals in the ^1H and ^{13}C NMR spectra. In particular, the presence of only two 2:1 *tert*-butyl singlets at 0.94 and 1.27 ppm, respectively, and three signals at 6.99 (d, J = 8.3 Hz, 1H), 6.30 (dd, J = 8.3, 2.4 Hz, 1H), and 6.40 ppm (d, J = 2.4 Hz, 1H), attributable to resorcinol ring, were a clear evidence of the displacement of a *t*-Bu

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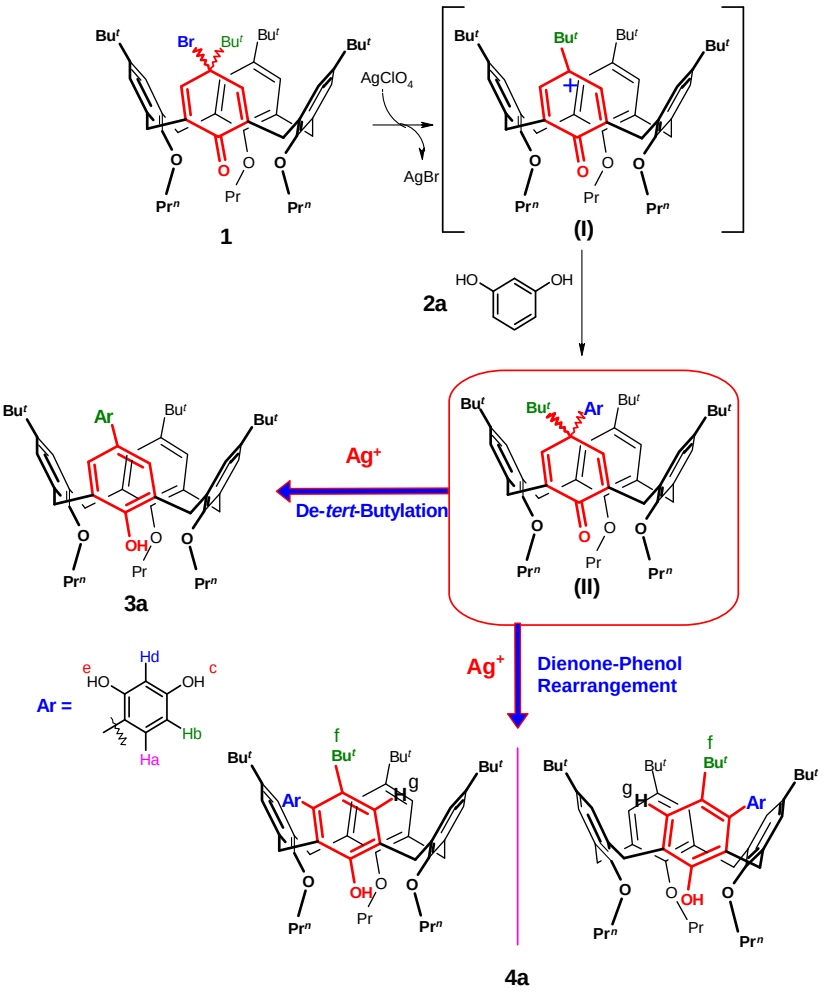


Scheme 1. Proposed mechanism for the formation of derivatives **3a** and **4a** via *p*-bromodienone route.

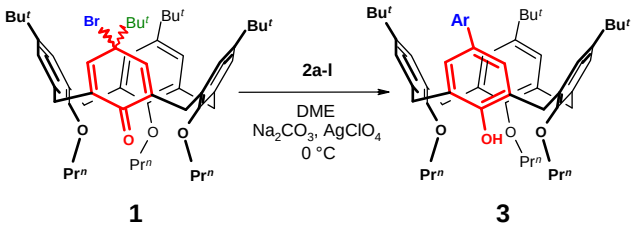
group by the aromatic moiety.[13] The linkage at the 4-position of resorcinol ring was readily deduced by the presence of the two *ortho*- and one *meta*-coupled signals. As expected, **3a** was very likely formed by the silver-mediated initial formation of aryloxenium cation **I** (Scheme 1), which was captured by resorcinol nucleophile through an electrophilic aromatic substitution to give C–C coupled dienone intermediate **II**. The latter then underwent de-*tert*-butylation to give re-aromatized derivative **3a** (Scheme 1).

Surprisingly, derivative **4a** showed an ^{1}H NMR spectrum in DMSO-d_6 (Fig. 1) consistent with an asymmetric calix[4]arene structure.[13] In fact, four *t*-Bu singlets were present at 0.88, 0.89, 1.15, and 1.31 ppm, while the diastereotopic $ArCH_2Ar$ protons appeared as eight partially overlapped doublets (Fig. 1).[13] In addition, the aromatic protons of calixarene skeleton gave six doublets with a typical *meta*-coupling (2.3 Hz) at 6.42 (1H), 6.52 (1H), 6.64 (1H), 6.67 (1H), and 7.23 ppm (2H, overlapped), and one singlet at 7.24 ppm attributable to the isolated ArH proton of the substituted phenol ring (Fig. 1).[13] Two OH singlets relative to resorcinol ring, were observed at low field (9.02 and 9.25 ppm), while the calixarene phenolic OH group was present at 6.35 ppm.[13] The 4-substitution of resorcinol ring was proved by an *ortho J*-coupling of aromatic H(a) proton (Scheme 1) at 6.83 ppm (d, J = 8.1 Hz, 1H) with the vicinal H(b) proton at 6.29 ppm (dd, J = 8.1 and 2.1 Hz, 1H) (COSY-45), which in turn was also *meta*-coupled with H(d) proton at 6.38 ppm (J = 2.1 Hz, 1H). These data were compatible with an asymmetric calix[4]arene structure in which a resorcinol and a *t*-Bu group were, respectively, *meta*- and *para*-linked to the calixarene phenol ring, or vice versa. In order to establish which of the two groups was *meta*-linked a 2D-NOESY study (250 MHz, C_6D_6, 298 K) was performed.[13] Diagnostic cross-peaks between the *t*-Bu(f) group (see Scheme 1) at 1.37 ppm and the isolated ArH(g) singlet at 7.51 ppm indicated their spatial proximity, only possible if the *t*-Bu and resorcinol groups were *para*- and *meta*-linked, respectively.

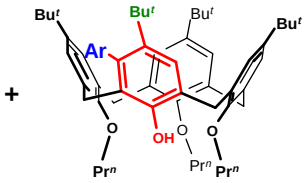
The formation of **4a** can be easily explained by assuming that intermediate dienone **II** undergoes a typical dienone–phenol rearrangement[15] to give *meta*-substituted calix[4]arene derivative **4a** (Scheme 1). Clearly, the rearrangement of dienone **II** occurs by 1,2-migration of resorcinol moiety, in accordance with the higher migratory aptitude of aromatic groups with respect to alkyl ones.[15,16] It is worth mentioning here that, to the best of our knowledge, this represents the first example of dienone–phenol rearrangement in calixarene chemistry. The asymmetric structure of **4a** coupled to its three-dimensional nature makes it inherently chiral and, consequently, it should be formed as a racemic mixture. The racemic nature of **4a** was evidenced by the doubling of several resonances in its ^{1}H NMR spectrum upon addition of Pirkle's reagent [(*S*)-(+)-(9-antryl)-2,2,2-trifluoroethanol] (Fig. 2).

The reaction of *exo/endo* mixture of **1** was extended to resorcinol dimethyl ether **2b** (Table 1, entry 'b'), which afforded *meta*-substituted, inherently chiral calix[4]arene **4b** in very low yield (5%) probably because this substrate was less activated, with respect to resorcinol **2a**, toward the electrophilic attack by aryloxenium cation **I** (Scheme 1). The reaction with particularly activated

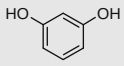
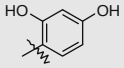
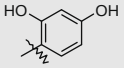
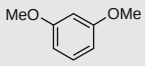
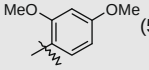
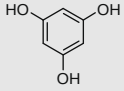
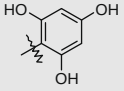
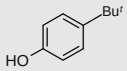
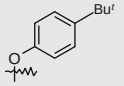
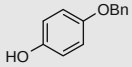
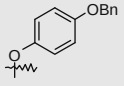
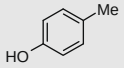
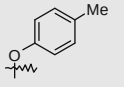
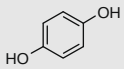
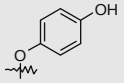
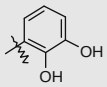
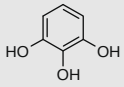
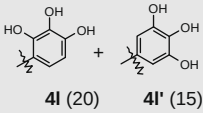
Table 1
Coupling products (yield, %) of *p*-bromo-dienone **1** with activated aromatic substrates **2a–l**



1 **3**



4

	2	**3** (Ar-)	**4** (Ar-)
(**a**)		 (10)	 (30)
(**b**)		–	 (5)
(**c**)		–	 (20)
(**d**)		–	 (20)
(**e**)[a]		–	 (10)
(**f**)		 (35)	–
(**g**)		 (20)	–
(**h**)		 (35)	–
(**i**)		 (20)	–
(**j**)		 (20)	 (10)
(**k**)		 (5)	–
(**l**)[b]		 (5)	 **4l** (20) **4l'** (15)

[a] In addition, derivative **5e** (Fig. 3) was also isolated in 20% yield.
[b] This reaction was conducted in the absence of Na_2CO_3.

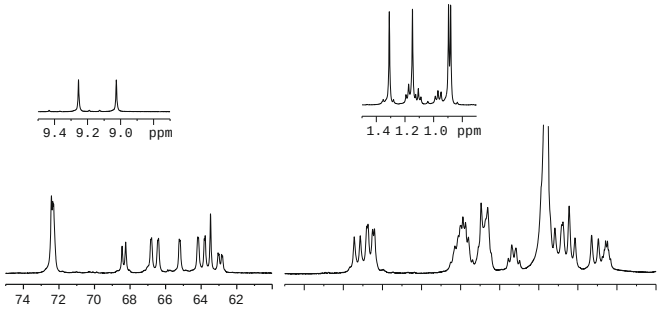


Figure 1. Significant portions of the ^{1}H NMR spectrum of derivative **4a** (DMSO-d_6, 400 MHz, 298 K).

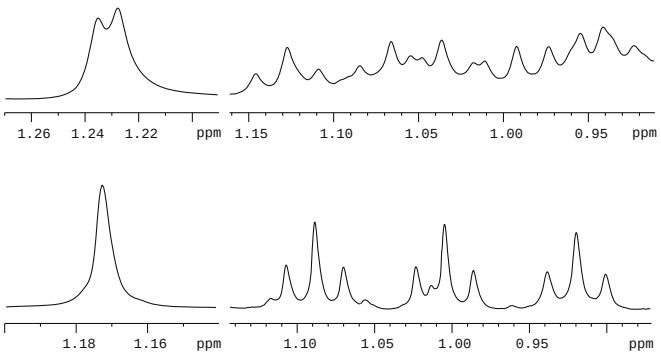


Figure 2. Portion of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of **4a** in the presence (top) or in the absence (bottom) of Pirkle's reagent.

aromatic nucleophiles, such as *N*-methylpyrrole **2c** and 2,6-dimethylphenol **2d** afforded both *meta*-substituted products **4c** and **4d** in 20% yield (Table 1, entries 'c and 'd').[13]

In all these instances the preferential 1,2-migration of the aromatic moiety was confirmed by detailed NOESY studies.[13] Thus, it appears clear that through the *p*-bromodienone route with highly activated substrates is possible to obtain *meta*-substituted calix[4]arenes,[17] which are of special interest because of the inherent chirality of calix[4]arene skeleton exploitable for enantiodiscrimination processes.[18] Interestingly, the analogous reaction with highly activated phloroglucinol (1,3,5-trihydroxybenzene) **2e** unexpectedly afforded, in addition to *meta*-substituted calix[4]-arene **4e** (10%; Table 1, entry 'e'), partial-cone derivative **5e** in 20% yield (Fig. 3),[13] in which the phloroglucinol moiety is linked to the calixarene oxygen atom at the *endo*-rim (also called *lower* or *narrow* rim). As demonstrated by chemical shift arguments and molecular modeling, the phloroglucinol moiety is self-filling the calix cavity in **5e** (Fig. 3). Evidently, this product is formed by electrophilic attack of the oxygen atom of aryloxenium cation **I** to phloroglucinol ring, after that a '*through-the-annulus*' ring inversion of dienone moiety has occurred. It is worth mentioning here

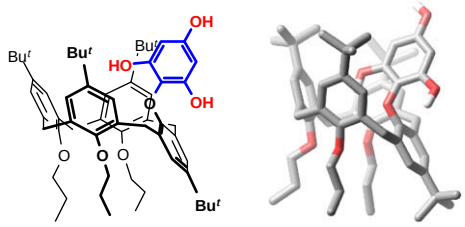


Figure 3. Chemical drawing of partial-cone **5e** (left) and its lowest MM3-energy structure ($CHCl_3$, GB/SA implicit model solvent) (right).

that this kind of O–C bond formation has been already observed in the chemistry of aryloxenium cations.[19]

In a second series of experiments we decided to examine the additional group of phenolic nucleophiles **2f–i** (Table 1). Thus, it was evidenced that phenols *para*-substituted with an alkyl (**2f** and **2h**), alkoxy (**2g**), and hydroxy (**2i**) group only gave C–O coupled *p*-aryloxy derivatives **3f–i** in 20–35% yield (Table 1). In these instances the nucleophilicity of OH group appears to be higher with respect to that of these aromatic rings which are less activated toward electrophilic aromatic substitution. A border line situation was obtained by the simple phenol **2j** which afforded both C–O coupled *para*-substituted calix[4]arene **3j** (20% yield) and C–C coupled *meta*-substituted derivative **4j** (10% yield; Table 1). Thus, it can be generalized that the *p*-bromodienone route with less activated substrates bearing a single OH group mainly affords C–O coupled, *para*-substituted derivatives through a nucleophilic attack of phenolic oxygen atom to aryloxenium cation **I**, in analogy with what observed with aliphatic alcohols.[8] Catechol **2k** afforded a second example of C–C coupled *para*-substituted derivative **3k** albeit in very low yield (5%; Table 1). Finally, pyrogallol **2l** gave mainly two isomeric C–C coupled *meta*-substituted calix[4]arenes **4l** and **4l'** (in 20% and 10% yield, respectively; Table 1) besides to a small amount (5%) of *para*-substituted derivatives **3l** C–O coupled at the central OH group. The formation of the latter derivative could be ascribed to the higher acidity of the central OH group due to H-bonding stabilization by the *ortho* ones.

In conclusion, we have demonstrated that the *p*-bromodienone route, previously applied to alcohols and carboxylates, can be extended to activated aromatic substrates. Depending on the reactivity of the substrate, aromatic moieties can be introduced at the *para*- or *meta*-position of calixarene aromatic ring, mainly through C–O or C–C coupling, respectively. In a few instances, examples of C–C coupling at the *para*-position and O–C coupling at the calixarene oxygen atom were also observed. The *p*-bromodienone route with highly activated aromatic substrates provides a practicable method for the synthesis of *meta*-substituted inherently chiral calix[4]arene derivatives, which can find interesting applications in enantiodiscrimination processes. In addition, the introduction of aromatic moieties at the calixarene *exo*-rim represents a novel procedure to obtain calix[4]arenes with enlarged aromatic central cavity, which could show enhanced recognition properties with respect to the native macrocycle. The potentiality of *p*-bromodienone route can be further expanded by using other N-, S-, and C-nucleophiles. Work along these lines is currently underway in our laboratory.

Supplementary data

Supplementary data (synthetic details, 1D and 2D ^{1}H and ^{13}C NMR data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.032.

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