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Novel 1,3-dipolar cycloaddition reactions of calix[4]bis(spirodienones): synthesis of isoxazolidine derived macrocycles

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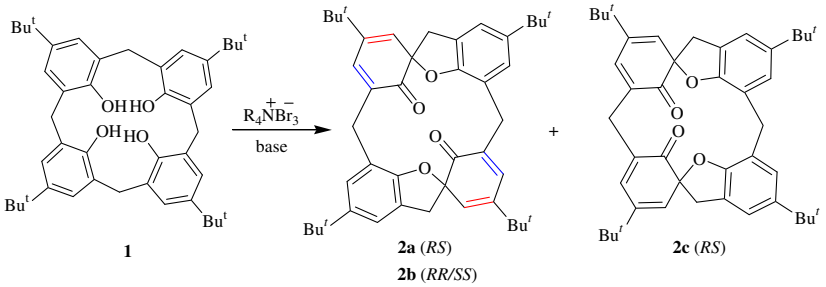
Abstract

Calix[4]bis(spirodienones) can perform as either 4π or 2π components in cycloaddition reactions with various carbo- and hetero-dienophiles and with 1,2-benzoquinones leading to the formation of highly functionalized macrocycles. In this Letter we report, highly regio- and stereoselective 1,3-dipolar cycloaddition reactions of a bis(spirodienone) derivative of calix[4]arene with nitrones that provide easy access to isoxazolidine derived macrocycles in excellent yields. These isoxazolidine derivatives can be considered as direct precursors of 1,3-amino alcohols.

Keywords: Calix[4]bis(spirodienone); *C*,*N*-Diarylnitrone; 1,3-Dipolar cycloaddition; Isoxazolidine

The calixarenes comprise an extensively studied class of macrocyclic and polyphenolic compounds that are strongly associated with host–guest chemistry.[1–5] The derivatization of calixarenes for the design of selective receptors for anions, cations and neutral molecules[6,7] has been largely done through the modification of the upper or lower rims. Lately an interesting molecular skeleton based on calixarenes, namely bis(spirodienones), was synthesized through the oxidative cyclization of the adjacent phenolic hydroxyls by Biali and Litwak (Scheme 1).[8] These spirodienones have been utilized further by the same group for the modifications of the calixarene skeleton that are otherwise difficult



1 **2a** (*RS*) **2b** (*RR/SS*) **2c** (*RS*)

Scheme 1. Oxidation of calix[4]arene.

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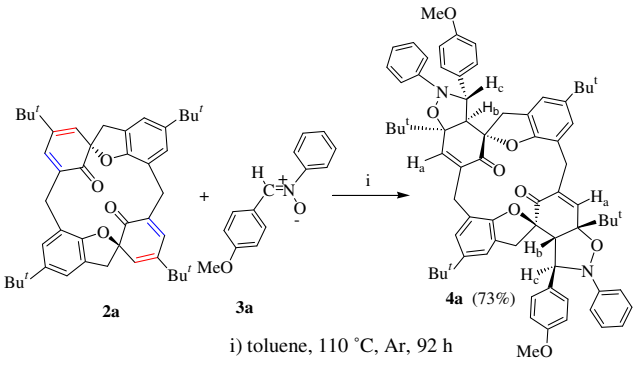
to achieve.[9–15] These are interesting molecular skeletons bestowed with two very reactive 2,4-cyclohexadienone systems giving leverage for further modification for the design of new macrostructures. Systematic studies from our group have shown their versatility as either 4π or 2π components in various Diels–Alder[16,17] and hetero Diels–Alder reactions.[18] We have also reported an addition reaction of the double bond shown in red with dichlorocarbene.[18] The reactivity of this double bond as the dienophile in cycloaddition with 1,2-benzoquinones and with dichlorocarbene has prompted us to investigate its reactivity towards 1,3-dipoles. Among various dipoles, nitrones are particularly attractive as they undergo facile [3+2] cycloaddition with alkenes to afford isoxazolidines which are direct precursors of 1,3-amino alcohols by reductive cleavage at the N–O bond.[19–22] From the standpoint of further functionalization of the calix[4]arene skeleton through cycloaddition, we undertook an investigation of the 1,3-dipolar cycloaddition reactions of the bis(spirodienone) with *C*,*N*-diarylnitrones and the results of our findings are presented in this Letter.

To the best of our knowledge, this is the first report on the 1,3-dipolar cycloaddition to the dienone moiety of a calix[4]bis(spirodienone). However, it should be mentioned that the 1,3-dipolar cycloaddition reactions of the azide substituents of calix[4]bis(azido)spirodienones with dimethyl acetylenedicarboxylate have been reported earlier by Simaan et al., which led to the formation of 1,2,3-triazole substituted products.[14]

We started our investigation by reacting the most stable isomer of calix[4]bis(spirodienone) **2a** with *C*-(4-methoxyphenyl)-*N*-phenylnitrone **3a**. Treatment of a solution of **2a** with 2 equiv of **3a** in dry toluene under reflux for 92 h yielded cycloadduct **4a** in good yield (Scheme 2).[23] Nitrones were prepared by the literature procedures.[24]

Product **4a** was characterized by conventional spectroscopic methods. In the IR spectrum, the carbonyl stretch appeared at 1659 cm^{-1}. The highly symmetrical nature of the product was ascertained from the ^1H NMR spectrum. In the ^1H NMR spectrum, the splitting patterns of the methylene groups were similar to those of **2a**. The proton,



Scheme 2. 1,3-Dipolar cycloaddition of **2a** with *C*-(4-methoxyphenyl)-*N*-phenylnitrone.

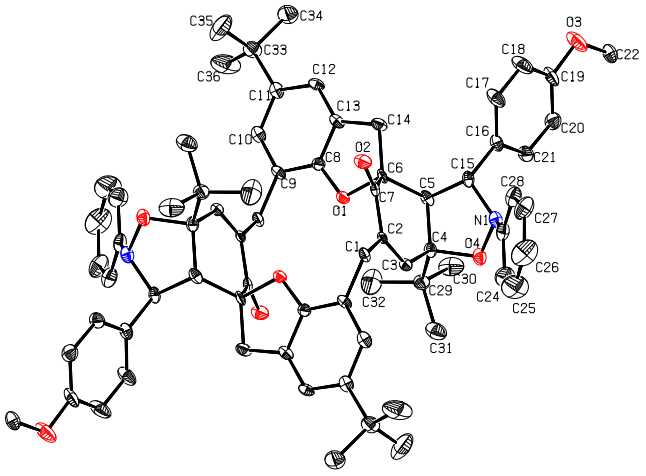
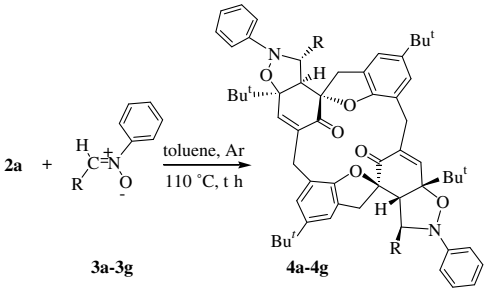


Fig. 1. ORTEP diagram of **4a** (hydrogen atoms omitted for clarity).

H_a, appeared as a singlet at δ 6.11. The doublet at δ 4.49 ($J = 4.8$ Hz) was assigned to the benzylic proton, H_c. The bridgehead proton, H_b, appeared as a doublet at δ 3.51 ($J = 4.5$ Hz). The sharp singlet at δ 3.77 corresponded with the methoxy protons of the nitrone. In the ^{13}C NMR spectrum, the carbonyl and spiro carbons appeared at δ 190.6 and 88.1, respectively. From the spectral data, it was confirmed that the addition occurred at the double bond (red in color) adjacent to the *tert*-butyl group as in the case of 1,2-benzoquinones.[17] The structure and regiochemistry of cycloadduct **4a** was further established by single crystal X-ray data (Fig. 1).[25]

To demonstrate the generality, the reaction was extended to other *C*,*N*-diphenylnitrones (Table 1). In all the reactions, the 5-isoxazolidines **4a–g** were obtained as single stereo- and regioisomers in very good to excellent yields. With *C*-(4-chlorophenyl)-*N*-phenylnitrone, the reaction was faster compared to the other nitrones and gave a

Table 1
The reactions of calix[4]bis(spirodienone) **2a** with various nitrones



Entry	R	Time (h)	Yield (%)
1	4-Methoxyphenyl, **3a**	92	**4a**, 73
2	4-Tolyl, **3b**	48	**4b**, 75
3	Phenyl, **3c**	72	**4c**, 90
4	4-Chlorophenyl, **3d**	44	**4d**, 99
5	4-Fluorophenyl, **3e**	80	**4e**, 98
6	4-Trifluorotolyl, **3f**	72	**4f**, 84
7	4-Nitrophenyl, **3g**	85	**4g**, 86

quantitative yield of cycloadduct **4d**. The reactivity was found to be different for different nitrones. Substituents at the *para* position of the *C*-phenyl group were found to have no significant influence on the reactivity.

[3+2] Dipolar cycloaddition reactions of nitrones to alkenes result in 4- or 5-substituted isoxazolidines, the regiochemistry being governed by the electronic nature of the alkenes. Electron rich or neutral alkenes give rise predominantly to 5-substituted isoxazolidines, whereas a reversal of regioselectivity is observed in the case of alkenes substituted with one or more powerful electron withdrawing groups such as cyano. This has been attributed to the lower orbital energies of alkenes with electron withdrawing groups favouring interaction between the HOMO of the dipole with the LUMO of the alkene which results in the formation of 4-substituted isoxazolidines. The calix[4]-bis(spirodienone) can be considered as a neutral alkene and, as expected a 5-substituted isoxazolidine is formed exclusively as confirmed by the X-ray crystal structure. It was also observed that the substituents at the *C*-phenyl have no significant effect on the reactivity but the rate of reaction was considerably influenced by these substituents.

In summary, we have introduced an isoxazolidine moiety to calix[4]bis(spirodienones) via 1,3-dipolar cycloaddition of nitrones. The bisadducts were obtained regiospecifically. Studies to transform the isoxazolidines to the highly functionalized macrocycles are underway and a detailed study of the reactivity of bis(spirodienones) with *C*-aryl, *N*-alkyl-nitrones and other 1,3-dipoles is in progress.

Acknowledgements

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23. *Typical experimental procedure*: To a solution of **2a** (50 mg, 0.08 mmol) in dry toluene (4 ml) was added **3a** (37 mg, 0.16 mmol). The reaction mixture was heated at 110 °C under an inert atmosphere for 92 h. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (eluent, 90:10 hexanes/EtOAc) to afford product **4a** in 73% yield as a white crystalline solid. The compound was crystallized from dichloromethane/acetonitrile mixture (3:1). Mp >300 °C. IR (KBr) ν_{max}: 2958, 1659, 1595, 1484, 1361, 1320, 1285, 1250, 1167, 876, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 0.92 (s, 18H, ^{t}Bu), 1.35 (s, 18H, ^{t}Bu), 1.96 (d, $J = 15.3$ Hz, 2H, $–CH_2–$), 2.98 (d, $J = 15.3$ Hz, 2H, $–CH_2–$), 3.44 (d, $J = 15.0$ Hz, 2H, $–CH_2–$), 3.51 (d, $J = 4.5$ Hz, 2H, bridgehead H), 3.77 (s, 6H, $–OCH_3$), 4.05 (d, $J = 15.3$ Hz, 2H, $–CH_2–$), 4.49 (d, $J = 4.8$ Hz, 2H, benzylic H), 6.11 (s, 2H, alkenyl H), 6.79 (m, 12 H, Ar H), 7.09 (s, 2H, ArH of calixarene), 7.20 (m, 4H, ArH), 7.35 (d, $J = 8.7$ Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) 190.6, 159.0, 152.7, 150.9, 144.2, 143.8, 140.5, 134.3, 128.6, 128.5, 126.9, 125.2, 120.7, 120.1, 114.2, 112.6, 90.0, 88.1, 71.6, 60.6, 55.2, 36.4, 34.6, 34.3, 33.2, 32.3, 31.9, 27.8, 26.9. MS (FAB): *m/z* calcd for $C_{72}H_{78}N_2O_8^+$: 1098.57. Found: 1098.10. Anal. Calcd for $C_{72}H_{78}N_2O_8$: C, 78.66; H, 7.15; N, 2.55. Found: C, 76.16; H, 6.84; N, 3.45.[26]
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25. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 657150.
26. We could not obtain satisfactory microanalytical data for **4a**. This seems to be a feature of several calixarene systems. See: Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790.