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Generation and stereocontrolled trapping of 3-phenylcyclopropene and its derivatives

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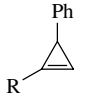
Selective methods for the preparation of 3-phenylcyclopropene and its 1-substituted derivatives are provided. The parent cyclopropene is readily trapped in (3+2)- and (4+2)-cycloadditions that lead to *exo*-3-phenyl-1,2-disubstituted cyclopropanes. *Ab initio* calculations suggest that the lowest energy conformation has the plane of the benzene ring perpendicular to the cyclopropene π-bond but with a low rotation barrier.

The unusual geometry and high strain energy of both saturated and unsaturated three-carbon rings[1,2] and the ability of substituents to change their structural parameters,[3] the regiochemistry of their reactions and, correspondingly, their biological properties are of interest to synthetic chemists, theoreticians and biochemists.[4–10] Cyclopropane and cyclopropene derivatives[11,12] are useful building blocks for syntheses. Cyclopropene itself, although stable indefinitely as a solid at liquid nitrogen temperature, and relatively stable at 325 °C diluted with helium,[13] undergoes dimerisation through an ene-reaction or oligomerisation even at –78 °C in a condensed phase.[13] Despite the enormous growth in the understanding of the chemistry of cyclopropenes, relatively little has been reported concerning systems having no substituents on the double bond and only one substituent at C-3. Indeed, although a number of examples have been reported, only 3-methylcyclopropene has been widely studied.[14] We consider the chemistry of 3-phenylcyclopropene **1**,[15] and its derivatives **2**–**5**.†

The initial precursor was 1,1,2-tribromo-3-phenylcyclopropane **6**, which was prepared as an *E*/*Z*-mixture from cinnamaldehyde by protection as the diethylacetal derivative followed by dibromocyclopropanation under phase-transfer conditions. Subsequent deprotection and oxidation of the aldehyde gave 2,2-dibromo-3-phenylcyclopropanecarboxylic acid. This acid was converted into tribromide **6** under Hunsdiecker conditions.‡ Reaction of **6** with 1.1 equiv. of methyllithium led to 1,2-dehalogenation with the formation of 1-bromo-3-phenylcyclopropene **4**,[16] which could be trapped if the reaction was carried out in the presence of diphenylisobenzofuran (DPIBF) as the *exo-anti*-adduct **11**.§ In the absence of the trap, the cyclopropene rearranged over 18 h at –30 °C to a mixture of allene **7** and acetylene **8**. Similar rearrangements have been reported for other monohalocyclopropenes.[17]



1–5

1 R = H
2 R = Me
3 R = C(OH)Me$_2$
4 R = Br
5 R = SiMe$_3$

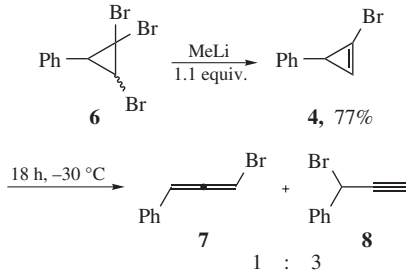
If the tribromide **6** was treated with 2.2 equiv. of MeLi at –80 °C, allowed to reach room temperature for 30 min, quenched with water or methanol at –40 °C and then concentrated at

† Low resolution mass spectra were measured using a Finnigan 8430 spectrometer with EI 70 eV unless otherwise stated. Accurate mass measurements refer to ^{79}Br isotopes unless stated and were carried out on a Micromass™ GCT spectrometer. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer. NMR spectra were recorded in $CDCl_3$ using Bruker AC250 and A500 spectrometers at 250 or 500 MHz (^{1}H) and 62.9 or 125 MHz (^{13}C). IR spectra were obtained in $CHCl_3$ solutions or as liquid films on a Perkin-Elmer 1600 FTIR spectrometer.

‡ Compound **6**, a mixture of two stereoisomers (*trans*/*cis* = 5): a colourless oil (found, M$^+$: 353.8076; $C_9H_7{}^{79}Br_2{}^{81}Br$ requires: 353.8077).

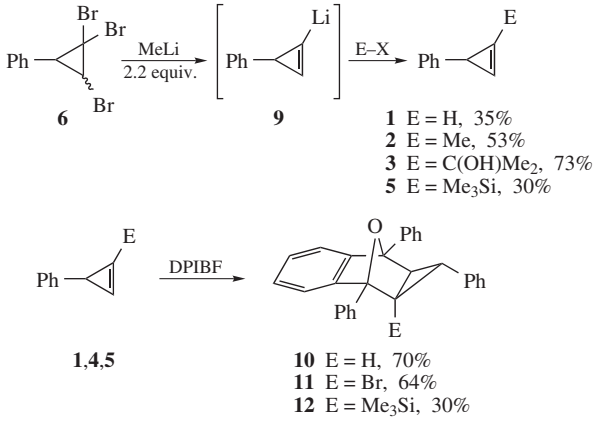
trans-Isomer, ^{1}H NMR, δ: 2.99 (d, 1H, *J* 7.0 Hz), 3.88 (d, 1H, *J* 7.0 Hz), 7.26–7.41 (m, 5H). ^{13}C NMR, δ: 33.2 (CH), 33.7 (C), 45.3 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 134.0 (C).

cis-Isomer, ^{1}H NMR, δ: 3.04 (d, 1H, *J* 9.8 Hz), 4.11 (d, 1H, *J* 9.8 Hz), 7.26–7.55 (m, 5H). ^{13}C NMR, δ: 31.6 (C), 36.7 (CH), 37.7 (CH), 128.0 (CH), 128.2 (CH), 130.2 (CH), 132.6 (C).



Scheme 1

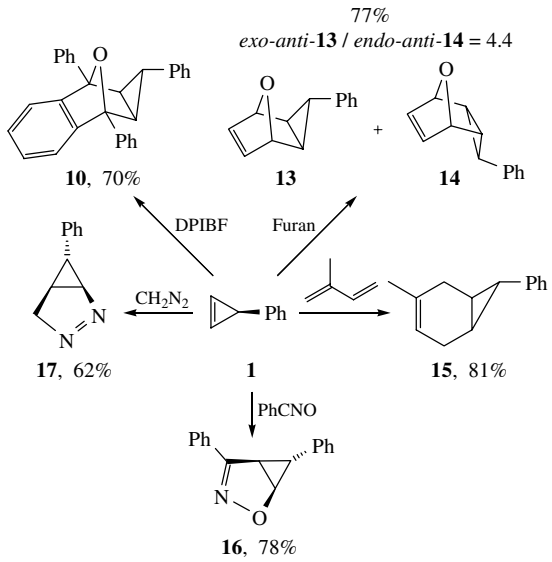
–20 °C, it gave 3-phenylcyclopropene **1** in 35 % yield, as determined by ^{1}H NMR.¶ This was trapped on addition of DPIBF as a single adduct, **10** (70% based on **6**).¶



Scheme 2

Cyclopropene **1** decomposed completely after a week in a $CDCl_3$ solution; no clear products could be identified. However, it could also be trapped efficiently in a range of other cycloadditions. In the case of the Diels–Alder adducts **10** and **13–15** with diphenylisobenzofuran, furan and isoprene, in each case the phenyl substituent was *exo*- on the cyclopropane ring. Similar selectivities have been observed for reactions of 3-methyl-3-phenylcyclopropene with DPIBF.[18] In contrast, this alkene forms *endo*-cycloadducts with up to 80 % selectivity, or exclusively in the case of *o*-benzoquinone, in reactions with cyclones.[18] With compound **1** the adducts with diazomethane and benzonitrile oxide also had the *exo*-stereochemistry.

Ab initio calculations at the B3LYP/6-31G* level suggest that 3-phenylcyclopropene **1**, like the 3-methyl-3-phenyl system, has a preferred bisected conformation; the rotation barrier for cyclopropene **1** is calculated to be 13.7 kJ mol^{-1}, whereas that for the 3-methyl-3-phenyl system is lower at 5.6 kJ mol^{-1}.[18] This probably reflects the lower stability of the bisected geometry



Scheme 3

caused by the introduction of the methyl group. In support of this, calculations for 3-*tert*-butyl-3-phenylcyclopropene suggest a preferred geometry in which the plane of the benzene ring is parallel to the cyclopropene π-bond. The HOMO of the preferred conformation of **1** is shown in Figure 1, alongside the calculated minimum energy structure.

Attempts to trap the intermediate 1-lithio-3-phenylcyclopropene **9** by the addition of acetone or benzaldehyde to the carbonyl group gave a good yield of cyclopropen-1-yl carbinol **3** in the former case[††] and no adduct in the latter. However, it could be trapped by reaction with methyl iodide at room temperature for 9 h, giving compound **2** in 53% yield.[‡‡] Trapping with methyl chloroformate or carbon dioxide led only to apparent polymers. However, reaction with TMSCl did give unstable cyclopropene **5**, which could be trapped in 30% yield by reaction with DPIBF, **12**.[§§]

Thus, efficient procedures have been developed for the preparation of 3-phenylcyclopropenes allowing the effect of the substituent on the reactivity of the cyclopropene π-bond to be studied.

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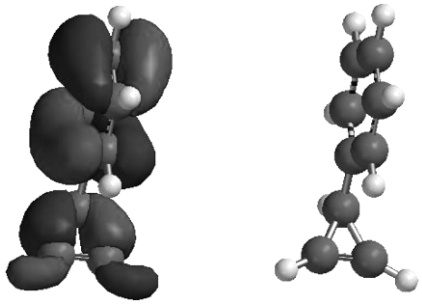

Figure 1

§ This was a white powder, mp 157–159 °C (MeOH) (found, M$^+$: 464.0757; $C_{29}H_{21}{}^{79}BrO$ requires: 464.0776). ^{1}H NMR, δ: 2.50 (d, 1H, *J* 4.4 Hz), 3.85 (d, 1H, *J* 4.4 Hz), 7.19 (m, 1H), 7.25–7.55 (m, 14H), 7.69 (m, 2H), 7.85 (m, 2H). ^{13}C NMR, δ: 37.3 (CH), 38.4 (CH), 50.9 (C), 89.1 (C), 92.4 (C), 119.8 (CH), 122.6 (CH), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 128.59 (CH), 128.62 (CH), 128.8 (CH), 128.9 (CH), 129.3 (CH), 129.6 (CH), 133.1 (C), 135.1 (C), 136.8 (C), 147.7 (C), 148.7 (C). IR ($CHCl_3$, ν_{max}/cm^{-1}): 3061 (m), 3029 (m), 1605 (m), 1497 (s), 1449 (s), 1304 (s), 1217 (s), 981 (s), 910 (w), 749 (s), 696 (s).

¶ 3-Phenylcyclopropene **1**. ^{1}H NMR, δ: 2.7 (s, 1H), 7.1–7.3 (m, 7H). ^{13}C NMR, δ: 19.5 (CH), 108.6 (CH), 125.6 (CH), 128.0 (CH), 128.6 (CH), 147.1 (C). IR (film, ν_{max}/cm^{-1}): 1646 (s). Phenylcyclopropene **1** was trapped on the addition of DPIBF (1.0 equiv.) as single adduct **10** (70%, based on tribromide **6**), a white powder, mp 156–158 °C (MeOH) (found, M$^+$: 386.1669; $C_{29}H_{22}O$ requires: 386.1671). ^{1}H NMR, δ: 2.20 (d, 2H, *J* 3.2 Hz), 3.30 (t, 1H, *J* 3.2 Hz), 7.11–7.76 (m, 19H). ^{13}C NMR, δ: 33.1 (CH), 35.2 (CH), 89.6 (C), 119.5 (CH), 126.1 (CH), 126.3 (CH), 126.4 (CH), 128.3 (CH), 128.40 (CH), 128.43 (CH), 128.6 (CH), 136.1 (C), 140.1 (C), 150.2 (C). IR ($CHCl_3$, ν_{max}/cm^{-1}): 3061 (m), 3030 (m), 1954 (w), 1810 (w), 1604 (m), 1497 (m), 1454 (s), 1342 (w), 1307 (s), 1248 (w), 1217 (m), 1059 (w), 981 (s), 905 (m), 747 (s), 698 (s).

†† This was stable for 3 weeks at –20 °C. The product contained some 4-hydroxy-4-methylpentan-2-one formed in the reaction conditions from acetone.

‡‡ Compound **2** was stable for two weeks at –20 °C when neat and for several months at that temperature in ethereal solution.

§§ Compound **5**, a colourless oil. ^{1}H NMR (–40 °C) δ: 0.28 (s, 9H), 2.61 (s, 1H), 7.17–7.56 (m, 6H). ^{13}C NMR, δ: –1.3 ($SiMe_3$), 20.2 (CH), 116.7 (C), 119.6 (CH), 124.7 (CH), 125.0 (CH), 127.7 (CH), 148.4 (C). IR (film, ν_{max}/cm^{-1}): 3059 (w), 3025 (m), 2955 (s), 2897 (m), 1693 (s), 1602 (m), 1492 (m), 1446 (s), 1407 (w), 1248 (s), 1070 (w), 841 (s), 756 (s), 698 (s). An optimised synthesis of this cyclopropene, as well as its unusual dimerisation, will be described elsewhere.

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