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PREPARATION OF ARYL CYCLOBUTENES UNDER MILD AND NEUTRAL CONDITIONS

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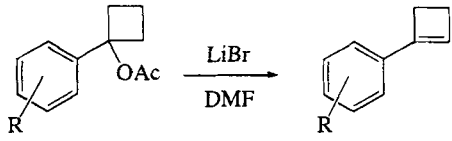
Abstract: Aryl cyclobutyl acetates were converted to the corresponding aryl cyclobutenes with lithium bromide in good yields (50-97%) and in high purity.

Cyclobutenes are mainly used in cycloaddition and photochemistry reactions.[1, 2] In general, the reported syntheses of cyclobutenes require either acidic[2a] or basic[3] conditions and, in some cases, high temperature may be necessary.[4] Our goal was to find suitable neutral conditions for the synthesis of cyclobutenes. Herein we wish to describe the lithium bromide assisted elimination of acetate to provide aromatic cyclobutenes (scheme 1).

SCHEME 1



1 **2**

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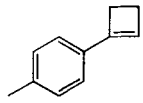
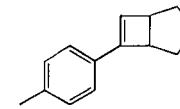
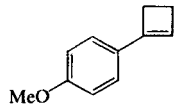
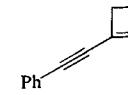
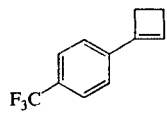
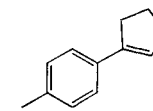
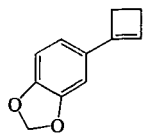
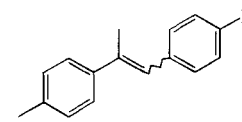
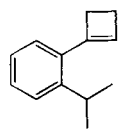
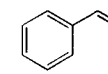
To establish the optimal reaction conditions, 1-(4-methylphenyl) cyclobutyl acetate was used as the initial probe. The reactions were run with a wide range of salts including LiCl, LiBr, LiI, $LiClO_4$, NaI and NaBr. Organic salts such as nBu_4NI were unreactive. Among the inorganic salts examined, lithium bromide showed the best overall results and was subsequently used as our standard salt in this investigation unless mentioned otherwise.[5] It was also observed that highly polar medium was required for the reaction to proceed at a reasonable rate. Thus, the reactions were performed with 10 equivalents of lithium bromide (5 M/salt) in DMF at 100 ^{0}C for 1 hour.[6] Under these conditions, the acetate readily eliminated to give the corresponding 1-(1-cyclobutenyl)-4-methylbenzene in 86% yield (entry 1). The purity of the crude compound was determined to be higher than 95% by proton nmr spectroscopy and no further purification was necessary.[7] The acetate was not the only group that could undergo elimination; benzoate and carbonate were also effective in the elimination reaction.

Electron-donating groups on the aromatic ring greatly accelerated the rate of reaction, though many side-products were produced. We found that with a lower temperature, typically 75 ^{0}C, formation of these side products could be reduced. With these less vigorous conditions, one can obtain the 1-(1-cyclobutenyl)-4-methoxybenzene (entry 2) in 89% yield. With the same conditions and without affecting the dioxolane moiety, the 5-(1-cyclobutenyl)-1,3-benzodioxole (entry 4) was isolated in 84% yield. No purification was necessary for these two compounds. On the other hand, electron-withdrawing substituents decreased the rate of the reaction and harsher conditions were needed. For

TABLE: Acetate Elimination with Lithium Bromide

ENTRY	PRODUCT	YIELD[a]	ENTRY	PRODUCT	YIELD[a]
1		86%[b]	6		90%[b]
2		89%[c]	7		59%[d,e]
3		50%[d]	8		92%[b]
4		84%[c]	9		97%[b,e]
5		90%[b]	10		70%[d]

[a] Isolated yield. [b] To the starting material in DMF was added lithium bromide (10 eq.). The reaction mixture was heated at 100 ^{0}C for 1 h. [c] To lithium bromide (10 eq.) in DMF at 75 ^{0}C was added the starting material. The mixture was heated at 75 ^{0}C for 1 h. [d] To the starting material in DMF was added lithium bromide (20 eq.). The reaction was heated at 140 ^{0}C for 1 h. [e] Isolated yield after hydrogenation.

example, 1-[4-(trifluoromethyl)phenyl] cyclobutyl acetate (entry 3) required 20 equivalents of lithium bromide and a temperature of 140 ^{0}C to obtain 50% yield of the desired compound. In this case, a purification over neutral alumina was done to obtain the pure product.

Sterically demanding substituents at the ortho position on the aromatic ring had no influence on the outcome of the reaction. For example, the 1-(2-

isopropylphenyl)cyclobutyl acetate (entry 5) gave, under the standard conditions, the expected cyclobutene in 90% yield. Likewise, substitution on the four membered ring (entry 6), did not change the rate of the reaction and afforded a high yield of the desired cyclobutene (90%).

Replacement of the aryl substituent by a secondary, tertiary or quaternary aliphatic group resulted in no elimination of the acetate. However, conjugated compounds such as 1-(2-phenyl-1-ethynyl) cyclobutyl acetate (entry 7) provided, after 90 min at 140 ^{0}C with 20 equivalents of lithium bromide, the conjugated cyclobutene in 59% yield. This compound was fully hydrogenated and purified by flash chromatography for characterization. The reaction proceeded even faster with a double bond but over reaction occurred and milder conditions were needed. Thus, at 75 ^{0}C and with 10 equivalents of lithium bromide, the expected conjugated cyclobutene was observed by proton nmr spectroscopy but was too unstable for isolation (not shown in the table).

The effect of ring size in the elimination reaction was also investigated. Replacing the cyclobutyl moiety by a cyclopentyl (entry 8) under the standard conditions, provided 1-(1-cyclopentenyl)-4-methylbenzene in 92% yield. With a cyclopropyl moiety, no elimination was observed even using harsher conditions.

With acyclic tertiary benzylic acetates (entry 9) a mixture of three olefins was isolated in 97% combined yield. To simplify the characterization, this mixture was hydrogenated to give the corresponding alkane. More drastic conditions were required with secondary benzylic acetate. To get a reasonable yield of product, the reaction required 20 equivalents of lithium bromide at 140 ^{0}C for 2 h. This provided the corresponding styrene in 70 % yield after flash

chromatography (entry 10). A similar result was obtained with (1-bromoethyl)benzene which corresponds to the replacement of the acetate group by a bromide. The fact that secondary benzylic bromide worked with this procedure does eliminate the possibility of an intramolecular reaction.

In conclusion, we have shown that 1-aryl cyclobutyl acetates are successfully used to prepare 1-aryl cyclobutenes in good yields (50-97%) and in high purity. This procedure provides pure products that often do not require further purification. To date all the experimental data on the acetate elimination reaction supports an E1 elimination mechanism.[8]

EXPERIMENTAL

Typical procedure for the preparation of 1-arylcyclobutanol: To a solution of 4-bromotoluene (12.84 g; 75.0 mmol) in 200 ml of THF at -78 ^{0}C was slowly added n-butyllithium (31.5 ml; 78.8 mmol; 2.5 M/hexanes). The reaction mixture was stirred at -78 ^{0}C for 15 minutes. A solution of cyclobutanone (5.0 g; 71.3 mmol) in 60 ml of THF was then added. The reaction was stirred 30 min at -78 ^{0}C then warmed to room temperature. The reaction was quenched with NH_4OAc sln, extract with EA and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered then evaporated to dryness. The compound was purified by flash chromatography on silica gel using 20% EA in hexanes to yield 9.833 g of the desired 1-(4-methylphenyl)cyclobutanol (85%).[2a]

ENTRY 1: 1-(4-methylphenyl)cyclobutyl acetate: To a solution of 1-(4-methylphenyl)cyclobutanol (3.323 g; 20.5 mmol) in 20 ml of CH_2Cl_2 at room temperature was successively added Et_3N (3.14 ml; 22.6 mmol), DMAP (125 mg)

and Ac_2O (3.9 ml; 41.0 mmol). After 2h at rt, the reaction was quenched with NH_4OAc sln, diluted with EA and washed with water and brine. The solution was dried over Na_2SO_4, filtered then evaporated. After purification by flash chromatography using 5% EA in hexanes, we obtained 3.824 g of 1-(4-methylphenyl)cyclobutyl acetate (91% yield): ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (1H, m), 1.93 (1H, m), 1.93 (3H, s), 2.31 (3H, s), 2.52-2.69 (4H, m), 7.13 (2H, d, *J*= 7.9 Hz), 7.36 (2H, d, *J*= 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.9, 21.5, 34.7, 81.9, 125.5, 128.7, 136.7, 139.5, 169.2; HRMS calcd for $C_{13}H_{16}O_2$ + H^+: 205.1228; Found: 205.1229. **1-(1-cyclobutenyl)-4-methylbenzene:** To a solution of 1-(4-methylphenyl)cyclobutyl acetate (102 mg, 0.5 mmol) in 1.0 mL of DMF was added lithium bromide (434 mg, 5.0 mmol). The reaction mixture was heated at 100 ^0C for 1 h. The reaction mixture was then cooled to room temperature, diluted in ethyl acetate and washed with water and brine. The solution was dried over sodium sulfate, filtered then evaporated to afford 62 mg of pure 1-(1-cyclobutenyl)-4-methylbenzene (86 %). ^1H and ^{13}C NMR are identical to the reported literature values.[2a]

ENTRY 2: 1-(4-methoxyphenyl)cyclobutyl acetate: ^1H NMR (400 MHz, $CDCl_3$): δ 1.68 (1H, m), 1.94 (1H, m), 1.95 (3H, s), 2.53-2.70 (4H, m), 3.80 (3H, s), 6.87 (2H, d, *J*= 8.8 Hz), 7.42 (2H, d, *J*= 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.5, 34.7, 54.9, 81.8, 113.3, 127.1, 134.4, 158.6, 169.3; HRMS calcd for $C_{13}H_{16}O_3$ + H^+: 221.1178; Found: 221.1177. **1-(1-cyclobutenyl)-4-methoxybenzene:** To a solution of lithium bromide (434 mg, 5.0 mmol) in 1.0 ml

of DMF at 75 °C was added 1-(4-methoxyphenyl)cyclobutyl acetate (110 mg, 0.5 mmol). The reaction was stirred at 75 °C for 1 h. After work-up, 71 mg of pure 1-(1-cyclobutenyl)-4-methoxybenzene was obtained in 89% yield. ^{1}H and ^{13}C NMR are identical to the reported literature values.[2a]

ENTRY 3: 1-[4-(trifluoromethyl)phenyl]cyclobutyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (1H, m), 1.98 (1H, m), 1.98 (3H, s), 2.62 (4H, m), 7.59 (4H, dd, *J*= 8.8 and 12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 21.3, 34.6, 81.5, 125.2 (q, *J*= 3.7 Hz), 125.4, 125.8, 129.3 (q, *J*= 32.3 Hz), 146.8, 169.3; HRMS calcd for $C_{13}H_{13}O_2F_3$ + H^+ - HOAc: 199.0735; Found: 199.0735. **1-(1-cyclobutenyl)-4-(trifluoromethyl)benzene:** To a solution of 1-[4-(trifluoromethyl)phenyl]cyclobutyl acetate (129 mg; 0.5 mmol) in 1.0 ml of DMF was added the lithium bromide (868 mg; 10.0 mmol). The mixture was stirred at 140 °C for 1 h. The corresponding cyclobutene was obtained after purification over neutral alumina using hexanes (50 mg; 50% yield). ^{1}H and ^{13}C NMR are identical to the reported literature values.[2a]

ENTRY 4: 1-(1,3-benzodioxol-5-yl)cyclobutyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (1H, m), 1.91 (1H, m), 1.94 (3H, s), 2.52-2.64 (4H, m), 5.89 (2H, s), 6.75 (1H, d, *J*= 7.9 Hz), 6.95 (1H, d, *J*= 7.9 Hz), 6.95 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.4, 34.7, 81.9, 100.9, 106.6, 107.6, 119.0, 136.4, 146.6, 147.4, 169.2; HRMS calcd for $C_{13}H_{14}O_4$ + H^+: 235.0970; Found: 235.0971. **5-(1-cyclobutenyl)-1,3-benzodioxole:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (2H, dd, *J*= 0.95 and 3.3 Hz), 2.73 (2H, t, *J*= 3.4 Hz), 5.91 (2H, s), 6.11 (1H, s), 6.73 (1H, d,

J= 7.96 Hz), 6.79 (1H, dd, *J*= 1.43 and 7.98 Hz), 6.84 (1H, d, *J*= 1.43 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 28.8, 100.9, 104.5, 108.0, 118.0, 125.0, 129.8, 145.8, 147.0, 147.7; HRMS calcd for $C_{11}H_{10}O_2$: 174.0681; Found: 174.0681.

ENTRY 5: 1-(2-isopropylphenyl)cyclobutyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (6H, d, *J*= 6.8 Hz), 1.70 (1H, m), 1.93 (3H, s), 1.97 (1H, m), 2.65 (2H, m), 2.78 (2H, m), 3.26 (1H, m, *J*= 6.8 Hz), 7.15 (1H, dt, *J*= 7.4 and 1.5 Hz), 7.25 (1H, dd, *J*= 7.4 and 1.2 Hz), 7.30 (1H, dt, *J*= 7.8 and 1.5 Hz), 7.57 (1H, dd, *J*= 7.8 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 21.7, 24.3, 29.1, 35.0, 83.6, 124.7, 127.0, 127.3, 128.2, 137.5, 147.9, 170.2; HRMS calcd for $C_{15}H_{20}O_2$ + H^+: 233.1542; Found: 233.1542. **1-(1-cyclobutenyl)-2-isopropylbenzene:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, d, *J*= 6.9 Hz), 2.57 (2H, t, *J*= 2.5 Hz), 2.95 (2H, t, *J*= 3.3 Hz), 3.48 (1H, m, *J*= 6.8 Hz), 6.23 (1H, s), 7.16-7.34 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 26.6, 29.3, 31.4, 125.0, 125.5, 126.9, 127.6, 130.7, 132.9, 145.8, 146.9; HRMS calcd for $C_{13}H_{16}$: 172.1252; Found: 172.1252.

ENTRY 6: 6-(4-methylphenyl)bicyclo[3.2.0]hept-6-yl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-1.63 (3H, m), 1.83 (2H, m), 2.00 (3H, s), 2.00-2.16 (2H, m), 2.32 (3H, s), 2.57 (1H, m), 2.90 (1H, m), 3.04 (1H, m), 7.14 (2H, d, *J*= 7.9 Hz), 7.32 (2H, d, *J*= 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.4, 25.6, 27.2, 32.3, 32.6, 38.2, 50.4, 79.0, 124.7, 128.9, 136.3, 142.2, 169.2. **6-(4-methylphenyl)bicyclo[3.2.0]hept-6-ene:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (2H, m), 1.57-1.80 (4H, m), 2.35 (3H, s), 3.16 (1H, dd, *J*= 3.3 and 7.1 Hz), 3.49

(1H, dd, *J*= 3.4 and 7.3 Hz), 6.10 (1H, s), 7.13 (2H, d, *J*= 7.9 Hz), 7.29 (2H, d, *J*= 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 23.1, 25.7, 26.3, 43.4, 45.6, 124.5, 126.6, 128.9, 131.1, 136.9, 145.7; HRMS calcd for $C_{14}H_{16}$: 184.1252; Found: 184.1252.

ENTRY 7: 1-(2-phenyl-1-ethynyl)cyclobutyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89-2.06 (2H, m), 2.04 (3H, s), 2.47 (2H, m), 2.66 (2H, m), 7.27 (3H, m), 7.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 21.1, 36.7, 72.1, 84.1, 89.2, 122.5, 128.0, 128.2, 131.6, 168.8; HRMS calcd for $C_{14}H_{14}O_2 + H^+$ - HOAc: 155.0861; Found: 155.0860. **1-(1-cyclobutenyl)-2-phenylacetylene:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (2H, m), 2.76 (2H, t, *J*= 2.28 Hz), 6.28 (1H, t, *J*= 1.34 Hz), 7.27 (3H, m), 7.42 (2H, m). **Hydrogenated compound**: ^{1}H and ^{13}C NMR are identical to the reported literature values;[9] HRMS calcd for $C_{12}H_{16}$: 160.1252; Found: 160.1256.

ENTRY 8: 1-(4-methylphenyl)cyclopentyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71-1.95 (4H, m), 1.97 (3H, s), 2.05 (2H, m), 2.30 (3H, s), 2.39 (2H, m), 7.10 (2H, d, *J*= 8.0 Hz), 7.25 (2H, d, *J*= 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 22.0, 23.2, 38.5, 91.4, 125.2, 128.7, 136.5, 140.6, 169.9. **1-(1-cyclopentenyl)-4-methylbenzene:** ^{1}H and ^{13}C NMR are identical to the reported literature values.[10]

ENTRY 9: 2-(4-fluorophenyl)-1-methyl-1-(4-methylphenyl)ethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, s), 2.00 (3H, s), 2.30 (3H, s), 3.16 (2H, dd,

J= 13.6 and 35.2 Hz), 6.83 (4H, d, *J*= 7.0 Hz), 7.07 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 22.1, 23.9, 48.1, 83.4, 114.3 (d, *J*= 21.0 Hz), 124.6, 128.7, 131.9, 132.0 (d, *J*= 7.7 Hz), 136.4, 141.0, 161.7 (d, *J*= 244.6 Hz), 169.4. **1-[2-(4-fluorophenyl)-1-methylethyl]-4-methylbenzene:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, d, *J*= 6.7 Hz), 2.35 (3H, s), 2.74-2.97 (3H, m), 6.93 (2H, t, *J*= 8.7 Hz), 7.00-7.13 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.1, 41.4, 44.0, 114.6 (d, *J*= 21.1 Hz), 126.7, 128.8, 130.3 (d, *J*= 7.8 Hz), 135.3, 136.3, 143.4, 161.1 (d, *J*= 243.3 Hz); HRMS calcd for $C_{16}H_{17}F$: 228.1314; Found: 228.1315.

ENTRY 10: 1-phenylethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (3H, d, *J*= 6.6 Hz), 1.99 (3H, s), 5.86 (1H, q, *J*= 6.6 Hz), 7.20-7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.9, 71.9, 125.8, 127.5, 128.2, 141.5, 169.7.

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5. The possibility of traces amount of acid was eliminated by the addition of sodium bicarbonate in the reaction mixture. This reaction gave the desired cyclobutene in high yield (>90%).
6. No reaction was observed under 3 M concentration and below.
7. Purification of cyclobutenes by standard flash chromatography on silica gel proved to be troublesome due to some decomposition.
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