Cyclopropanation of alkenes using hypervalent iodine reagents

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Dedicated to Professor Anastasios Varvoglis on the occasion of his 65th birthday

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Abstract

The addition of bisnucleophiles to alkenes is mediated by hypervalent iodine compounds. This reaction, either performed stepwise or in a one – pot procedure, is a cyclopropanation of alkenes yielding 1,1-dicyanocyclopropane derivatives as reaction products.

Keywords: Addition reactions, alkenes, cyclopropanes, electrophiles, hypervalent iodine compounds

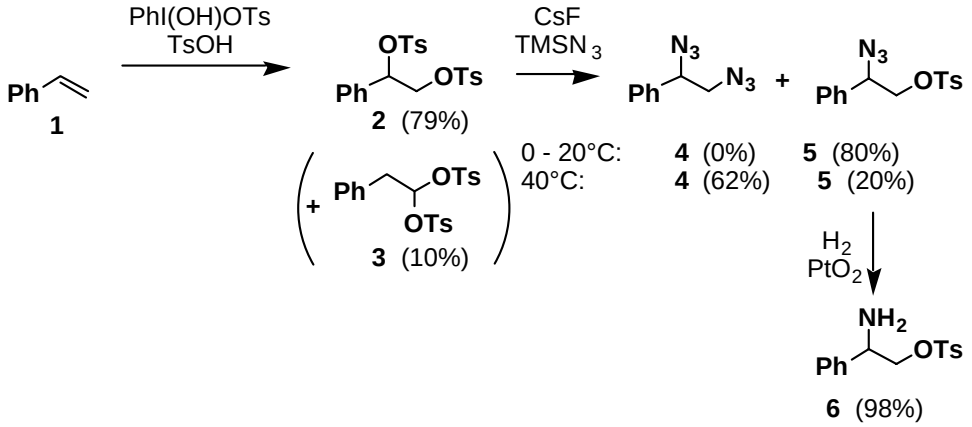
Introduction

Hypervalent iodine compounds are well known for their mild oxidative properties. But a wide range of different reactions using these compounds is possible.[1] They can be used as electrophilic reagents and various functionalizations of unsaturated systems have been carried out. Oxidative additions to double bonds have been carried out using a wide range of different nucleophiles. Recently the co-introduction of non-equivalent nucleophiles has been investigated intensively.[2]

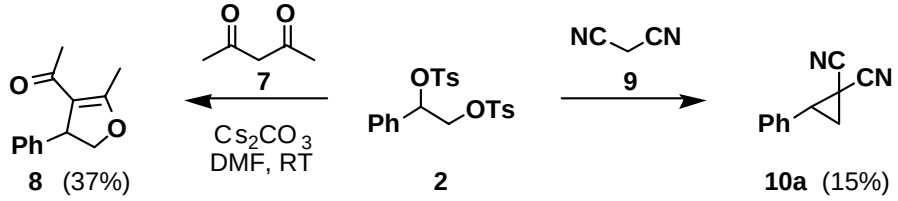
Results and Discussion

General Procedures. [Hydroxy(tosyloxy)iodo]benzene was first reported in 1970[3] and is often called Koser's reagent.[4] This reagent is known to ditosylate alkenes efficiently and one can use either two equivalents of the reagent or one equivalent together with one equivalent *para*-toluenesulfonic acid. Compound **2** is obtained from styrene **1** in good yield together with a rearranged side product **3**. We have replaced either one or both of the tosylates in **3** with an azide depending on the reaction conditions. Using chiral [hydroxy(tosyloxy)iodo]arene derivatives we

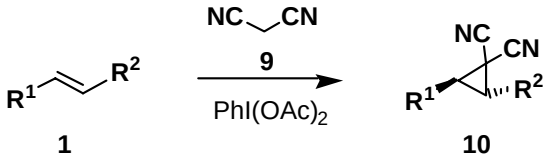
were able to synthesize ditosylate **2** in up to 65 % *ee*.[5] Being a clean S_N2 process, the resulting azides **4** and **5** have the same enantiomeric excess and can be reduced to the corresponding amine like **6** easily.[6]



We then explored the possibility of adding bisnucleophiles to compound **2**. Addition of acetylacetone **7** lead to the formation of a five-membered heterocycle which has been synthesized earlier by different routes.[7] After initial attack of the central carbon atom in **7** at the benzylic position, the enolate oxygen of the 1,3-dicarbonyl compound attacks as a second nucleophile to give the dihydrofurane derivative **8** in 37% yield. Malonodinitrile **9** as bisnucleophile, however, generated the cyclopropane derivative **10** in low yields.



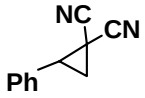
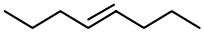
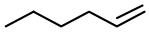
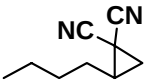
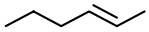
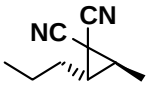
As the electrophilic activation of double bond with (diacetoxyiodo)benzene is known for a long time, we tried to directly introduce the bisnucleophile thus performing the cyclopropanation in one step starting from the corresponding alkene.[8] We were pleased to find an even higher yields in the corresponding 1,1-dicyanocyclopropane derivatives of type **10**. The results are summarized in the following table. Other styrene compounds have been investigated as well, but α-methylstyrene and β-methylstyrene did not yield any product under the reaction conditions.



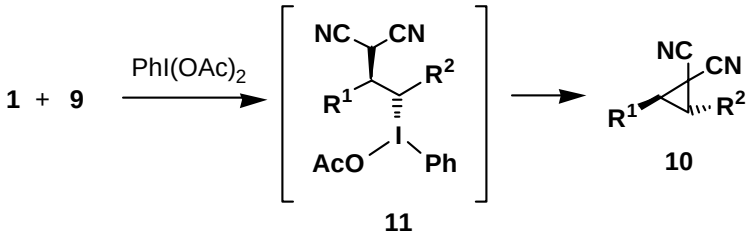
1,1-Dicyanocyclopropanes of type **10** can be prepared also by other, more complicated routes[9] and have been used for various photochemical investigations.[10]

Intermolecular[11] (photochemical) and intramolecular[12] (thermal) cyclopropanations using iodonium ylides as carbene precursors are known and several examples have been reported. We could not observe any reaction between (diacetoxyiodo)benzene and malonodinitrile under the reaction conditions. Even prolonged heating gave an unchanged ^{1}H NMR spectrum

Table 1. Cyclopropanation of Alkenes

Entry	Alkene **1**	Product **10**	Yield
1	 **1a**	 **10a**	35%
2	 **1b**	 **10b**	24%
3	 **1c**	 **10c**	31%
4	 **1d**	 **10d**	33%

with no indication of iodonium ylide formation. We therefore assume a stepwise reaction as shown below. The malonodinitrile attacking the activated alkene in a first step to yield an intermediate of type **11**. The hypervalent iodine species is then acting as a hypernucleofuge allowing the second attack to form the cyclopropane derivative. Within the limits of alkene purities, the cyclopropanation reaction is stereoselective and by NMR analysis no *cis*-isomers (Table 1, entries 2 and 4) have been detected.



In conclusion, we have developed a cyclopropanation of alkenes leading to 1,1,-dicyanocyclopropane derivatives. Although the yields are still quite low, work concerning the optimization of the reaction is in progress.

Experimental Section

Hydroxy(tosyloxyiodo)benzene (100 mg, 0.26 mmol) and *p*-toluenesulfonic acid (46 mg, 0.26 mmol) were dissolved in methylene chloride (6 mL) and cooled to 0°C. Styrene (54 mg, 0.52 mmol) is dropwise added to the suspension and after stirring for 28 h at rt the solvent was removed and the residue purified by flash-chromatography (*tert*-butyl methyl ether: pentane 1: 2). Compound **2** (46 mg, 79 %) and **3** (6 mg, 10 %) were obtained.

2. mp.: 117 - 120 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.64 (m, 4H), 7.22 (m, 9H), 5.56 (dd, *J* = 7.5, *J* = 4.2, CH), 4.16 (m, 2H, CH_2), 2.44 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 145.1 (s), 144.8 (s), 133.6 (s), 133.4 (s), 133.3 (s), 129.9 (d, 2C), 129.6 (d, 2C), 129.3 (d), 128.7 (d, 2C), 127.9 (d, 2C), 127.9 (d, 2C), 126.8 (d, 2C), 80.0 (t), 70.1 (d), 21.7 (q), 21.6 (q), IR ($CHCl_3$): ν = 3373, 3037, 1600, 1497, 1370, 1263, 1176, 1136, 1051, 1016, 916, 867, 814, 562 cm^{-1}; MS(FAB + KCl): 485 (32%, M + K), 447 (4, M+H), 275 (97), 155 (100), 104 (19), 91 (56), 83 (9), 69 (12), 57 (24), 43(22).

3. mp.: 93 - 96 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57 (m, 4H), 7.19 (m, 9H), 6.37 (t, *J* = 5.7, 1H, CH), 3.11 (d, *J* = 5.7, 2H, CH_2), 2.40 (s, 6H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 145.1 (s, 2C), 132.9 (s), 132.3 (s, 2C), 129.7 (d), 129.6 (d, 4C), 128.5 (d, 2C), 127.8 (d, 4C), 127.2 (d), 99.5 (d), 41.9 (t), 21.6 (q, 2C); IR ($CHCl_3$): ν = 3036, 2929, 1598, 1496, 1455, 1380, 1096, 1072, 1019, 956, 908, 853, 814 cm^{-1}.

Cesium fluoride (81 mg, 0.5 mmol) under Ar is treated with a solution of trimethylsilyl azide (81 mg, 0.7 mmol) in DMF (2 mL). After 20 min stirring at rt a solution of **2** (80 mg, 0.18 mmol) in DMF (2 mL) is added at 0 °C. After stirring for 50 h at 40 °C sat. $NaHCO_3$ (4 mL) and water (10 mL) are added. After extraction (ethyl acetate, 2 x 20 mL) the combined organic phases are dried with magnesium sulfate, the solvent was removed and the residue purified by preparative TLC (*tert*-butyl methyl ether : pentane 1 : 10) to obtain compound **4** (21 mg, 62 %) as a yellow oil together with **5** (20 %).

4. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 4.67 (dd, *J* = 8.2, *J* = 5.2, 1H, CH) 3.47 (m, 2H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 136.3 (s), 129.1 (d, 2C), 129.0 (d), 126.9 (d, 2C), 65.5 (t), 56.0 (d); IR ($CHCl_3$): ν = 2927, 2492, 2104, 1439, 1454, 1018, 907 cm^{-1}; MS(EI): 132 (40, M-2N_2), 104 (76), 77(100), 63 (7), 51 (35), 39 (9); HPLC: λ = 220 nm, hexane : 2-propanol 95 : 5, 0.5 ml/min, Chiracel OD, t_{R1} = 10.28 min, t_{R2}= 20.90 min.

Cesium fluoride (160 mg, 1.0 mmol) under Ar is treated with a solution of trimethylsilyl azide (166 mg, 1.4 mmol) in DMF (2 mL). After 20 min. stirring at rt a solution of **2** (163 mg, 0.3 mmol) in DMF (2 mL) is added at 0 °C. After stirring for 42 h at rt sat. $NaHCO_3$ (4 mL) and water (10 mL) are added. After extraction (ethyl acetate, 2 x 20 mL) the combined organic phases are dried with magnesium sulfate, the solvent was removed and the residue purified by flash-chromatography (*tert*-butyl methyl ether: pentane 1: 2) to obtain compound **5** (91 mg, 80 %) as a yellow oil.

5. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 1.8, 2H), 7.29 (m, 7H), 4.77 (dd, *J* = 8.5, *J* = 4.4, 1H, CH), 4.21 (m, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 145.1 (s), 134.6 (s), 132.5 (s), 129.9 (d, 2C), 129.1 (d), 129.0 (d, 2C), 127.9 (d, 2C), 127.0 (d, 2C), 71.6 (t), 63.9 (d), 21.6 (q); IR ($CHCl_3$): ν = 2109, 1599, 1454, 1367, 1177, 1097, 982 cm^{-1}; MS(FA(B): 318 (13%, M+H), 290 (19, M-N_2), 275 (27, M- N_3), 155 (37), 137 (85), 118 (68), 104 (30), 91 (100), 77(5), 69 (64), 57 (86), 43 (83), HPLC: λ = 254 nm, hexane : 2-propanol 95 : 5, 0.5 ml/min, Chiracel OD, t_{R1} = 30.48 min, t_{R2} = 38.72 min.

Compound **5** (65 mg, 0.21 mmol) and platinum dioxide (1.5 mg) are dissolved in methanol (1 mL) and trifluoroacetic acid (2 μL) and hydrogenated (1 atm) for 2 h at 0 °C and for 18 h at rt. After filtration (celite) the solvent was removed and **6** was obtained (60 mg, 98%) as a white solid.

6. mp. 102 - 104 °C; ^{1}H-NMR (300 MHz, $CDCl_3$, CD_3OD): δ = 7.66 (m, 2H), 7.25 (m, 7H), 4.55 (m, 1H, CH), 4.35 (m, 2H, CH_2), 2.38 (s, 3H, CH_3); MS(FA(B): 292 (100, M+H), 275 (11), 249 (7), 211 (13), 155 (27), 120 (20), 106 (15), 91 (21), 79 (6), 69 (7), 57 (14), 43 (13).

To a suspension of cesium carbonate (755 mg, 2.7 mmol), **2** (400 mg, 0.9 mmol) in DMF (10 mL) was added acetylacetone (453 mg, 4.5 mmol). After 15 h stirring at rt sat. $NaHCO_3$ (5 mL) and water (30 mL) were added. After extraction (ethyl acetate, 3 x 30 mL) the combined organic phases are dried with magnesium sulfate, the solvent was removed and the residue purified by flash-chromatography (*tert*-butyl methyl ether: pentane: 5) to obtain compound **8** (68 mg, 37 %) as a colorless oil.

8. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 5H), 4.74 (dd, *J* = 9.0, *J* = 10.1, 1H, CH), 4.37 (ddd, *J* = 5.1 Hz, *J* = 10.1 Hz, *J* = 0.9 Hz, 1H, CH_2), 4.27 (dd, *J* = 5.1 Hz, *J* = 9.0 Hz, 1H, CH_2), 2.36 ppm (d, *J* = 0.9 Hz, 3H, CH_3-C=C), 1.58 ppm (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 194.9 (s), 169.6 (s), 143.6 (s), 128.8 (d, 2C), 127.1 (d, 2C), 127.1 (d) , 116.1 (s), 78.8 (t), 48.9 (d), 29.6 (q), 15.0 (q) / IR ($CHCl_3$): 3006, 1662, 1587, 1492, 1454, 1383, 1322, 1126, 1079, 998, 939, 917, 628 cm^{-1}; MS 202 (100, M), 159 (30), 145 (39), 128 (20), 115 (33), 91 (20), 77 (21), 65 (11), 63 (12), 51 (25); HPLC: λ = 278 nm, hexane: 2-propanol 95 : 5, 0.5 ml/min, Chiracel OD, t_{R1} =19.30 min , t_{R2} = 23.55 min.

(Diacetoxyiodo)benzene (300 mg,0.93 mmol) and malono dinitrile (92 mg, 1.4 mmol) are dissolved in methylene chloride (4 mL) and the alkene (1.86 mmol) is added at –78 °C. After stirring for 24 h at rt the solvent is removed the residue purified by flash-chromatography (*tert*-butyl methyl ether : pentane 1 : 5) to obtain compound **10**.

Alkene: styrene, **10a**: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 3H), 7.29 (m, 2H), 3.30 (t, *J* = 9.1, 1H), 2.26 (dd, *J* = 9.1, *J* = 1.0, 2H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$ / TMS), δ = 130.5 (s), 129.5 (d), 129.2 (d, 2C), 128.3 (d, 2C), 115.3 (s), 113.0 (s), 35.1 (d), 29.7 (t), 22.4 (s); IR ($CHCl_3$): ν = 3029, 2400, 2250, 1521, 1474, 1421, 1045, 1029, 927 cm^{-1}; MS(EI): 168 (100%, M), 140 (57), 114 (28), 103 (9), 89 (11), 77 (20), 63 (13), 51 (21); HPLC: λ = 220 nm; hexane : 2-propanol 80 : 20, 0.5 ml/min, Chiracel OD, t_{R1} = 47.47 min, t_{R2} = 62.03 min.

Alkene: *E*-4-octene, **10b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.55 (m, 10H), 0.95 (t, *J* = 7, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$ / TMS), δ = 116.7 (s, 2C), 38.0 (d, 2C), 35.7 (s), 32.3 (t, 2C), 21.7 (t, 2C), 14.0 (q, 2C); IR ($CHCl_3$): ν = 3021, 2966, 2885, 2243, 1464, 1383, 1222 cm^{-1}.
Alkene: 1-hexene, **10c**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 5.1, 3H, CH_3), 1.3-1.6 (m, 7H), 1.89 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$ / TMS), δ = 112.7 (s, 2C), 37.0, 33.7, 31.1, 30.4, 19.9, 13.4, 10.9; IR ($CHCl_3$): ν = 2945, 2855, 2243, 1453cm^{-1}.
Alkene: *E*-2-hexene, **10d**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 4.8, 3H, CH_3), 1.35 (d, *J* = 6.16, 3H, CHC*H*$_3$), 1.50 (m, 5H), 1.71 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$ / TMS), δ = 114.6 (s, 2C), 38.9, 32.9, 32.2, 31.3, 21.7, 15.2, 13.9; IR ($CHCl_3$): ν = 2966, 2865, 2243, 1461, 1383, 1257, 1057 cm^{-1}.

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