CYCLOADDITION OF 1-METHOXY-3-TRIMETHYLSILYLOXYBUTADIENE WITH HALOGENATED CARBONYL COMPOUNDS

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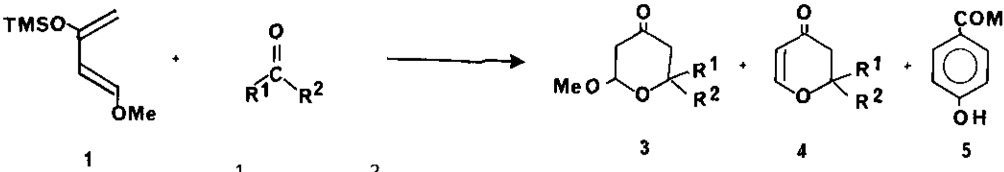
Abstract-Cycloadditions of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**) with halogenated carbonyl compounds (**2**) yielded corresponding substituted tetrahydro- and/or dihydropyran-4-ones (**3** and/or **4**). Lewis acids were found to be effective as catalysts. Reactions with less reactive carbonyl compounds (**2c,d**) afforded p-hydroxyacetophenone (**5**) produced by cyclodimerization of **1**. Stereochemistry of the adducts was deduced by ^{1}H nmr spectroscopy.

Among the reported synthetic methods of substituted dihydropyran-4-ones,[1] the cycloaddition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**)[2] with simple aldehydes holds an outstanding position,[3-5] and it has been successfully applied to the syntheses of carbohydrates and related natural products.[6-8] The cycloadditions of **1** with some β-keto esters have also been known to give corresponding cycloadducts, however, the reactions with ketones were reported to be totally unsuccessful.[9] In continuation of our synthetic work on dihydropyran derivtives,[10] *we examined the reaction of* **1** with some halogenated carbonyl compounds.

The reaction of **1** with trichloroacetaldehyde (**2a**) gave an initial cycloadduct, 2-methoxy-6-trichloromethyl-4-trimethylsilyloxy-5,6-dihydro-2H-pyran, almost quantitatively. The other regioisomer was not detected. On standing the cycloadduct, crystalline 2-trichloromethyl-2,3-dihydropyran-4-one (**4a**) was obtained by elimination of methanol and the silyl protecting group. Addition of methanol to **4a** yielded 2-methoxy-6-trichloromethyltetrahydropyran-4-one (**3a**) as a mixture of two diastereomers; one diastereomer was produced almost exclusively. Inspection of the ^{1}H nmr characteristics of the major isomer revealed that the H_2 (δ =5.30) has $J_{2,3}$=1.5 and 3.5 Hz, and H_6 (δ =4.50) has $J_{5,6}$=3.5 and 10.5 Hz. Thus the major diastereomer should be assigned to one having an equatorial C_6 trichloromethyl and an axial C_2 methoxy groups, as expected from the anomeric effect observed for 2-alkoxytetrahydropyran derivatives. The reaction of chloroacetaldehyde (**2b**) with **1** did not give the corresponding initial adduct, but 2-chloromethyl-2,3-dihydropyran-4-one (**4b**) was obtained in a 18 % yield as a sole adduct.[11] The presence of zinc iodide catalyst[12] increased the yield of **4b** to 65 %.



2a	R^1=CCl_3,	R^2=H
b	CH_2Cl,	H
c	CF_3,	Ph
d	$CHCl_2$	Ph

The reactions of **1** with aliphatic or aromatic ketones were reported to be unsuccessful,[9] however, that with phenyl trifluoromethyl ketone (**2c**) took place despite somewhat sluggish, and two cycloadducts, 2-methoxy-6-phenyl-6-trifluoromethyltetrahydropyran-4-one (**3c**, 34 %) and 2-phenyl-2-trifluoromethyl-2,3-dihydropyran-4-one (**4c**, 11 %) were afforded. The cycloadduct of the former type (**3**) was not obtained in other cases. ^1H and ^{13}C nmr spectra showed that **3c** consisted of two diastereomers (2:1). The major isomer was determined to possess an axial methoxy group at C_2 (H_2, dd, δ =4.64, $J_{2,3}$=2.5 and 3.5 Hz) and the minor isomer was thought to possess an equatorial methoxy group (H_2, t, δ =4.48, $J_{2,3}$=3.5 Hz). Zinc iodide increased the yield of **4c** at the expense of that of **3c**. Interestingly a considerable amount of p-hydroxyacetophenone (**5**) was isolated only in the zinc iodide catalyzed reaction. This means that **5** was produced by a Lewis acid catalyzed cyclodimerization of **1**, followed by elimination of methanol, and of the silyl protecting group, and final aromatization.[13] No regioisomer of **5**, m-hydroxyacetophenone, was detected at all.

A less reactive ketone, dichloromethyl phenyl ketone (**2d**), did not react with **1** even in the presence of zinc chloride, and **5** was isolated as a sole product.

Table 1. Reaction of 1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**) with Halogenated Carbonyl Compounds (**2**)

Carbonyl compd.	Catalyst	Time (h)^a	Yields of products (%)			
			3	**4**	**5**	recovered **2**
2a	-	3^b	0	100	0	0
2b	-	18	0	18	0	0
	ZnI_2	24	0	65	0	0
2c	-	48	34	11	0	10
	ZnI_2	48	0	20	28	24
2d	$ZnCl_2$	48	0	0	28	100

a) At room temperature. b) At 0 °C

EXPERIMENTAL

Infrared spectra were recorded on a JASCO IRA-3 spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded on JEOL PMX-60 and JNM FX-90Q spectrometers. Chemical shifts are given in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on an ESCO EMD-05A spectrometer. Melting points were measured on a Yanagimoto micro hot plate apparatus and are uncorrected. All commercial chemicals were used as obtained without further purification, except for solvents which were purified and dried, where appropriate, before use by standard methods. Chloroacetaldehyde (**2b**) was prepared by heating (85-86 °C) chloroacetaldehyde hemihydrate (predistilled, bp 85.5 °C), and the vapor was passed through a preheated (115-120 °C) calcium chloride tube, and then cooled. The condensed **2b** was immediately dissolved in anhydrous tetrachloromethane, and the solution was stored in a dark cold chest.[14]

2-Trichloromethyl-2,3-dihydropyran-4-one (4a). To an ice-cooled solution of trichloroacetaldehyde (**2a**, 410 mg, 2.8 mmol) in tetrachloromethane (20 ml), 340 mg (1.98 mmol) of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**) was added and the solution was stirred for 3 h at room temperature. After evaporation of the solvent, 2-methoxy-6-trichloromethyl-4-trimethylsilyloxy-5,6-dihydro-2*H*-pyran was obtained in a nearly quantitative yield as a clear liquid. From this liquid, **4a** was crystallized out on standing in a refrigerator; 92 % after recrystallization from hexane: mp 107-109 °C; ms(m/z), 218, 216, 214(M^+), 181, and 179; ir(KBr), 1670, 1600, 1280, 1230, 1050, 810, and 780 cm^{-1}; ^1H nmr($CDCl_3$) δ 2.98(1H, d, J=11 Hz), 3.00(1H, d, J=7 Hz), 4.82(1H, dd, J=7 and 11 Hz), 5.56(1H, d, J=6 Hz), and 7.45(1H, d, J=6 Hz); ^{13}C nmr ($CDCl_3$), δ 37.93, 86.12, 97.47, 107.82, 161.21, and 189.16. Anal. Calcd for $C_6H_5O_2Cl_3$, C, 33.45, H, 2.34, Cl, 49.36; Found, C, 33.61, H, 2.47, Cl, 49.43.

2-Methoxy-6-trichloromethyl-4-trimethylsilyloxy-5,6-dihydro-2*H*-pyran. Clear oil; ir(film), 1680, 1650, 1600, and 1080 cm^{-1}; ^1H nmr($CDCl_3$) δ 0.25(9H, s), 2.47(2H, m), 3.51(3H, s), 4.51(1H, dd, J=6.5 and 9.0 Hz), 4.89(1H, m), and 5.21(1H, d, J=4.0 Hz).

2-Methoxy-6-trichloromethyltetrahydropyran-4-one (3a). Reaction of **4a** (100 mg, 0.46 mmol) with methanol (10 ml) for several days at room temperature yielded **3a** (72 mg, 63 %) after silica gel chromatographic separation (hexane-ethyl acetate, 6:1): a diastereomeric mixture (approximately 100:3): mp 55.5-56.5 °C; ms(m/z), 250, 248, 246(M^+), 219, 217, 215, 190, 188, and 186 ; ir(KBr), 2940, 1740, 1130, 1040, 950, and 770 cm^{-1}; ^1H nmr($CDCl_3$) δ 2.42-3.12(4H, m), 3.49(3H, s), 4.50(1H, dd, J=3.5 and 10.5 Hz), and 5.30(1H, dd, J=1.5 and 3.5 Hz); ^{13}C nmr($CDCl_3$, chemical shifts for a minor diastereomer are given in parentheses) δ 42.81 (and 41.9), 45.60 (and 46.1), 55.67 (and 56.6), 78.05, 96.10, 99.66 (and 100.5), and 200.94. Anal. Calcd for $C_7H_9O_3Cl_3$, C, 33.97, H, 3.67, Cl, 42.97; Found, C, 33.96, H, 3.60, Cl, 43.07.

2-Chloromethyl-2,3-dihydropyran-4-one (4b). A zinc iodide (60 mg) catalyzed reaction of chloroacetaldehyde (**2b**, 110 mg, 1.2 mmol) with **1** (200 mg, 1.2 mmol) was carried out in benzene (5 ml) at room temperature for 24 h to give **4b** (110 mg, 65 %) after silica gel column chromatographic separation (hexane-ethyl acetate, 6:1): bp 140 °C/8 mmHg; ms(m/z), 148, 146(M^+), 121, and 111; ir(KBr) 1680, 1600, 1420, 1290, 1240, and 1060 cm^{-1}; ^1H nmr($CDCl_3$) δ 2.53(1H, dd, J=4.5 and 17 Hz), 2.76(1H, dd, J=13 and 17 Hz), 3.79(1H, dd, J=5 and 8.5 Hz), 3.80(1H, dd, J=4.5 and 8.5 Hz), 4.68(1H, dddd, J=4.5, 4.5, 5, 13 Hz), 5.44(1H, d, J=6 Hz), and 7.40(1H, d, J=6Hz); ^{13}C nmr($CDCl_3$) δ 39.04, 44.90, 77.83, 107.19, 162.29, and 190.73. Anal. Calcd for $C_6H_7O_2Cl$, C, 49.17, H, 4.81; Found, C, 49.05, H, 5.02.

2-Phenyl-2-trifluoromethyl-2,3-dihydropyran-4-one (4c). Phenyl trifluoromethyl ketone (**2c**, 610 mg, 3.5 mmol) was allowed to react with **1** (400 mg, 2.3 mmol) in tetrachloromethane (20 ml) at room temperature for 48 h. Usual work up and chromatographic separation (hexane-ethyl acetate, 6:1) gave recovered **2c** (63 mg, 10 %), 4-methoxy-3-buten-2-one (40 mg, 17 %), **4c** (60 mg, 11 %), and 2-methoxy-6-

phenyl-6-trifluoromethyltetrahydropyran-4-one (**3c**, 216 mg, 34 %).

3c: a diastereomeric mixture (approximately 2:1); bp 148-149 °C/7 mmHg; ms(m/z) 274(M^+), 234, 205, and 172; ir(KBr), 2950, 1740, 1170, 1050, and 700 cm^{-1}. Anal. Calcd for $C_{13}H_{13}O_3F_3$, C, 56.94, H, 4.78; Found, C, 57.02, H, 4.92.

A major isomer of **3c**: ^1H nmr(C_6D_6) δ 2.33(1H, d, J=2.5 Hz), 2.41(1H, d, J=3.5 Hz), 2.83(3H, s), 3.19(2H, m), 4.64(1H, dd, J=2.5 and 3.5 Hz), and 7.0-7.25(5H, m); ^{13}C nmr($CDCl_3$) δ 42.65, 44.13, 56.51, 100.07, 124.88($J_{C,F}$=285.6 Hz), 126.26, 128.29, 129.05, 131.22, 137.94, and 200.97.

A minor isomer of **3c**: ^1H nmr(C_6D_6) δ 1.96(1H, d, J=3.5 Hz), 2.07(1H, d, J=3.5 Hz), 3.09(2H, m), 3.18(3H,s), 4.48(1H, t, J=3.5 Hz), and 7.25-7.5(5H, m); ^{13}C nmr ($CDCl_3$) δ 42.10, 44.35, 55.70, 98.80, 111.57($J_{C,F}$=277.7 Hz), 127.21, 128.76, 129.38, 130.30, 135.55, and 200.07.

4c: mp 86.6-88.1 °C; ms(m/z) 242(M^+), 224, and 172; ir(KBr), 1690, 1610, 1280, 1200, 1180, 1020, and 700 cm^{-1}; ^1H nmr($CDCl_3$) δ 3.29(2H, s), 5.40(1H, d, J=6.5 Hz), 7.31(1H, d, J=6.5 Hz), and 7.44(5H, s); ^{13}C nmr($CDCl_3$) δ 39.37, 108.58, 123.47($J_{C,F}$=283.2 Hz), 127.32, 128.40, 128.86, 130.11, 131.79, 158.96, and 187.62. Anal. Calcd for $C_{12}H_9O_2F_3$, C, 59.51; H, 3.75; Found, C, 59.22; H, 3.77.

Reaction of dichloromethyl phenyl ketone (2d) with 1. A zinc chloride (1 ml of a 1 molar ether solution) catalyzed reaction of **1** (411 mg, 2.4 mmol) with **2d** (490 mg, 2.6 mmol) in benzene(20 ml) at room temperature for 48 h revealed, after usual work up and chromatographic separation (hexane-ethyl acetate, 6:1), almost quantitative recovery of the starting ketone. No cycloadduct was detected, however, p-hydroxyacetophenone (**5**, 45 mg, 28 %) was isolated instead.

5[15]: mp 105-106 °C; ms(m/z) 136(M^+) and 121; ir(KBr) 3350, 1670, 1610, and 1580 cm^{-1}; ^1H nmr($CDCl_3$) δ 2.25(3H,s), 6.86(2H, d, J=8 Hz), 7.81(2H, d, J=8 Hz), and 8.17(1H, s, br).

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11. 4-Methoxy-3-buten-2-one (26 %) was also obtained.

12. Zinc chloride and Yb(fod)$_3$ were also effective as the catalysts; the yield of **4b** being 47 % (1 h) and 46 % (72 h), respectively.

13. A referee pointed out another possible pathway for the formation of **5**, which composed of an initial double Michael addition of **1** with 4-methoxy-3-buten-2-one and subsequent elimination of methanol. At present the authors have no sound evidence to confirm the mechanism.

14. We are indebted to Miss M. Nishinaka for ms determination and microanalysis.

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