Tetrahedron Letters No.23, pp. 1849-1851, 1969. Pergamon Press. Printed in Great Britain.

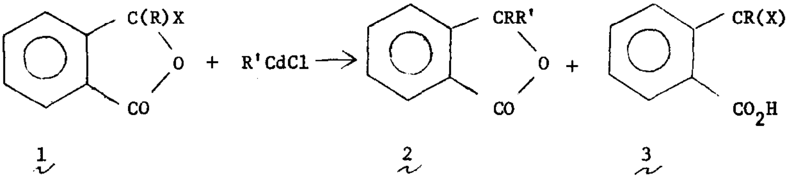
FORMATION OF OPTICALLY ACTIVE 3-METHYLPHTHALIDE BY A DISPLACEMENT WITH METHYLCADMIUM CHLORIDE

Paul R. Jones and Carl J. Jarboe

Department of Chemistry, Parsons Hall, University of New Hampshire, Durham, N.H. 03824

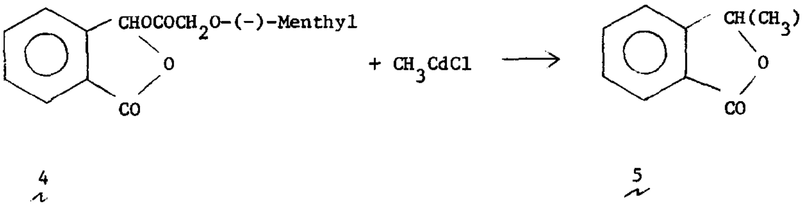
(Received in USA 13 January 1969; received in UK for publication 13 April 1969)

We wish to report the first example of formation of an optically active product by displacement at a saturated carbon atom effected by an organocadmium reagent. The work was undertaken as part of a continuing effort to gain an understanding of the unusual reaction (1) (Equation 1), in which a phthalide (**1**) with a 3-substituent undergoes



(1)

effective displacement by the cadmium reagent of either X or acyloxy with formation, respectively, of **2** or **3**. The substrate finally chosen for stereochemical study was 3-(-)-menthoxyacetoxyphthalide (**4**). This substrate **4** was prepared (33%) in pyridine



(2)

from phthalaldehydic acid (2) and (-)-menthoxyacetyl chloride (3): mp 85-86°; ir (4a) (double mull) 1775 (ester C=O) and 1780 cm^{-1} (lactone C=O); nmr (4b) (CCl_4), δ 0.50-3.50 (series of multiplets, 19, (-)-menthyl protons), δ 4.13 (s, 2, C=O-C<u>H</u>$_2$-O-), δ 7.38 (s, 1, -C<u>H</u>OCO) and δ 7.50-8.00 (m, 4, aromatic). <u>Anal</u>. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.47; H, 7.67. $[\alpha]^{24}_{578}$ - 71.3±0.5* (<u>c</u> 2.2, C_2H_5OH). Higher rotations were also measured at 546, 436, and 405 mμ(4c). Methylcadmium chloride in ether converted 4 to a mixture of neutral material, as yet unidentified, and (+)-R-3-methylphthalide (5) (5). The latter was isolated in 38% yield, free of the other product and starting material (36% by nmr analysis with dioxane as an added internal standard), through a sequence of steps involving distillation, saponification, acid-catalyzed cyclization, extraction, and a final distillation. Compound 5 was identical with (±)-3-methylphthalide (1b) with regard to ir, nmr, and tlc; bp 101° (0.9 mm); ir (neat) 1760 cm^{-1} (C=O); nmr (neat) δ 1.67 (d, 3, <u>J</u> = 7 Hz, CHC<u>H</u>$_3$), δ 5.71 (q, 1, <u>J</u> = 7 Hz, C<u>H</u>CH$_3$), δ 7.40-8.00 (m, 4, aromatic); $[\alpha]^{25}_{578}$ + 2.28 ± 0.07 (<u>c</u> 7.3, CH_3OH).

Similar results were obtained in a second experiment: $[\alpha]^{24}_{578}$ + 2.18 ± 0.02 (<u>c</u> 5.4, CH_3OH).

Whatever the diastereomeric composition of 4, the formation of optically active product excludes total racemization as the stereochemical course of the reaction. An estimation of the optical purity of 5 can be made by comparison of our rotations, converted to sodium D-line values by means of the Drude equation, with the rotation published by Nagai <u>et al</u>. ($[\alpha]_{590}$ - 30.7° $[CH_3OH]$). By these calculations, 5 from our two experiments has an optical purity of 7.2% and 6.8%, respectively. The degree of reaction stereospecificity, however, depends on the diastereomeric composition of 4.

Although our isolation (precipitation from water and two recrystallizations from ethanol) could have provided a single diastereomer of 4, it is more likely in our opinion that the starting material is a mixture of diastereomers. In spite of this, its rotation and mp were unchanged after multiple recrystallizations from a variety of solvents; and no resonance doubling of the C-3 diastereotopic hydrogen is evident in the nmr spectrum. The absence of any resonance doubling (6) is attributed to the

---

*Average Deviation

large distance between the two asymmetric centers. By contrast, 3-(-)-menthoxyphthalide (**1**, R = H; X = O-(-)Menthyl) exhibits two singlets for the C-3 diastereotopic protons with a separation of about 6 Hz. The rotation of recovered 4 was essentially unchanged, $[\alpha]^{32}_{578}$ - 70.1±1.0 (*c* 2.6, C_2H_5OH), an observation in support of closely similar activation energies for both diastereomers or the presence of a single diastereomer in **4**. The two observations combined--formation of optically active product and recovery of starting material with unchanged rotation--render unlikely any case where **4** consists of equal amounts of the two diastereomers.

The present case is an interesting example of a stereospecific reaction of two dissymmetric diastereomers with a nondissymmetric reagent (7). Experimental distinction between retention and inversion for this displacement will require prior determination of the absolute configuration of **4**.

REFERENCES

(1) (a) P. R. Jones and S. L. Congdon, *J. Am. Chem. Soc.*, **81**, 4291 (1959); (b) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (c) F. N. Jones and C. R. Hauser, *ibid.*, **27**, 3364 (1962); (d) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967).

(2) We thank Dow Chemical Company, Midland, Michigan, for a generous supply of this acid.

(3) M. T. Leffler and A. E. Calkins, "Organic Syntheses," Coll. Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1955, pp 547-548.

(4) (a) Infrared spectra were determined with a Perkin-Elmer 337 grating spectrophotometer; (b) Nmr spectra were determined with a Varian A-60 spectrometer; (c) Rotations were determined with a Zeiss photoelectric polarimeter. Values are the average of at least two determinations.

(5) U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, **21**, 1701 (1965).

(6) J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968), and references cited therein.

(7) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, New York, 1966, p. 122 ff.