Cyclic Imides. IX. Displacement of Halide from *N*-Substituted 3-Halophthalimides by Methoxide Ion (1,2)

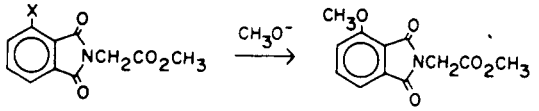
Rosemary G. Fowler, Lyman R. Caswell (3), and Lily I. Sue (4)

Department of Chemistry, The Texas Woman's University, Denton, Texas 76204

Received March 26, 1973

In an earlier paper in this series (5), it was reported that sodium methoxide acts upon *N*-substituted 3-nitrophthalimides to give nucleophilic displacement of nitrite to form *N*-substituted 3-methoxyphthalimides. This displacement reaction did not occur with *N*-substituted 4-nitrophthalimides. Studies of the activity toward displacement of a substituent on the phthalimide moiety have now been extended to a number of halogenated phthalimides, specifically, methyl 3-chlorophthalimidoacetate (Ia), methyl 3-fluorophthalimidoacetate (Ib), *N*-phenyl-3-chlorophthalimide (IIIa), *N*-phenyl-3-fluorophthalimide (IIIb), and methyl 4-chlorophthalimidoacetate (V).

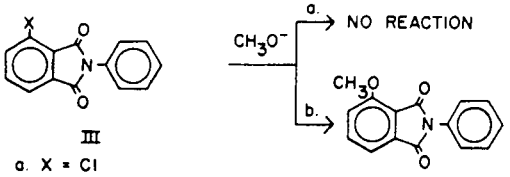
Action of refluxing methanolic sodium methoxide on either Ia or Ib, at a mole ratio of 1 to methoxide of 1 to 1.5, resulted in displacement of halide to form methyl 3-methoxyphthalimidoacetate (II). To obtain comparable yields of II required four hours of refluxing for displacement of chloride from Ia, but only five minutes for displacement of fluoride from Ib. Under the same conditions, IIIb was converted in a comparable yield to *N*-phenyl-3-methoxyphthalimide (IV) in the time required to heat the reaction mixture from room temperature to the boiling point. In contrast, IIIa failed to undergo displacement of chloride, even on prolonged heating.



I

a. X = Cl
b. X = F

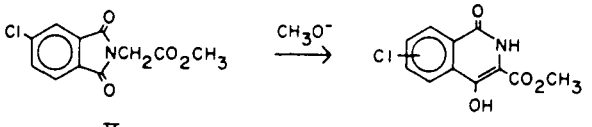
II



III

a. X = Cl
b. X = F

IV



V

VI

The displacement reaction was not observed with methyl 4-chlorophthalimidoacetate (V). Like its nitro analog, V was isomerized by sodium methoxide to form, in very poor yield, a product whose spectral behavior was consistent with that of products (VI) of the Gabriel-Colman rearrangement.

Neither the halogens nor the nitro group are normally subject to nucleophilic displacement from the benzene ring. This lack of reactivity is attributable to resonance interactions between substituent electrons and the ring π-electron cloud, shortening and strengthening the bond between the substituent and the ring (6). Such interactions must be suppressed or absent in the cases of the 3-nitro- and 3-fluorophthalimides, and reduced in the cases of the 3-chlorophthalimides. Suppression of resonance interaction in 3-nitrophthalimide has already been demonstrated by spectral evidence (7).

Steric effects do not provide a satisfactory explanation for the susceptibility of the 3-substituent to displacement. The order of decreasing ease of displacement is $F > NO_2 >> Cl$, while the order of decreasing size is $NO_2 >> Cl > F$. The ease of displacement of the nitro group, moreover, decreases with increasing bulkiness of the *N*-substituent (5), suggesting that steric effects hinder the displacement reaction. Since there is effective nucleophilic displacement only of the two most strongly electronegative groups, F and NO_2, and since the cyclic imide moiety is also strongly electron attracting, we suggest that the suppression of resonance interaction results from an inductive competition between the electron-withdrawing tendencies of the imide moiety and the substituent. It is interesting to note that the same order of ease of displacement of substituents has been observed (8) with pyridine and quinoline derivatives. The heterocyclic nitrogen atom and the cyclic imide moiety evidently have comparable activating effects.

EXPERIMENTAL (9)

Methyl Halophthalimidoacetates (IV).

The methyl halophthalimidoacetates were prepared from the halophthalimidoacetic acids (10) by esterification with methanol in the presence of anhydrous hydrogen chloride (11). The products were recrystallized from methanol, giving: methyl 3-chlorophthalimidoacetate (Ia), 76%, m.p. 105-106°; methyl 3-fluorophthalimidoacetate (Ib), 66%, m.p. 114-115°; and methyl 4-chlorophthalimidoacetate (V), 93%, m.p. 92.5-93.5°.

Anal. Calcd. for $C_{11}H_8ClNO_4$: C, 52.09; H, 3.18; Cl, 13.98; N, 5.52. Found for Ia: C, 51.75; H, 3.13; Cl, 13.70; N, 5.45. Found for V: C, 52.08; H, 3.14; Cl, 13.85; N, 5.28.

Anal. Calcd. for $C_{11}H_8FNO_4$: C, 55.70; H, 3.38; N, 5.91. Found: C, 55.50; H, 3.23; N, 5.78.

N-Phenyl-3-chlorophthalimide (IIIa).

The procedure of Marriott and Robinson (12) gave an 86% yield of *N*-phenyl-3-chlorophthalimide, m.p. 189-191°; reported (12) m.p. 189-190°; ir spectrum (potassium bromide): 3300, 1710, 1635, 1490, 1450, 1375, 1125 (C-Cl stretch), 1110, 890, 750, 730, and 700 cm^{-1}.

N-Phenyl-3-fluorophthalimide (IIIb).

To a refluxing solution of 5.81 g. (0.035 mole) of 3-fluorophthalic anhydride in 50 ml. of glacial acetic acid was added 6.5 g. (0.07 mole) of aniline during ten minutes. The mixture was refluxed three hours, cooled, diluted with 50 ml. of carbon tetrachloride, chilled, and filtered. The precipitate was rinsed with carbon tetrachloride and recrystallized from methanol to give 7.5 g. (89%) *N*-phenyl-3-fluorophthalimide, m.p. 151-152°; ir spectrum (potassium bromide): 3300, 1715, 1640, 1490, 1475, 1380, 1240 (C-F stretch), 1110, 965, 755, 740, and 700 cm^{-1}; nmr spectrum (deuteriochloroform): δ 7.55 (5 protons), 7.4 (3 protons, broad).

Anal. Calcd. for $C_{14}H_8FNO_2$: C, 69.71; H, 3.32; N, 5.81. Found: C, 69.52; H, 3.13; N, 5.67.

Methyl 3-Methoxyphthalimidoacetate (II).

To a solution of 0.03 mole of sodium in 50 ml. of absolute methanol was added 0.02 mole of Ia or Ib. The stirred mixture was refluxed four hours in the case of Ia, or five minutes in the case of Ib. The mixtures were cooled, acidified with 1 *N* hydrochloric acid, and filtered. After recrystallization from 1:1 benzene-hexane, the products melted at 147-148° and did not depress the melting point of authentic (5) methyl 3-methoxyphthalimidoacetate (II). The ir spectra were also identical. The yield of II from Ia was 41%; from Ib, 39%; nmr spectrum (deuteriochloroform): δ 7.2-7.9 (multiplet, 3 aromatic protons), 4.5 (singlet, CH_2), 4.06 (singlet, 3-OCH_3), 3.8 (singlet, ester OCH_3).

N-Phenyl-3-methoxyphthalimide (IV).

To a solution of 0.03 mole of sodium in 50 ml. of absolute methanol was added 4.82 g. (0.02 mole) IIIb. The temperature was raised to the boiling point, producing a white precipitate. The mixture was cooled to room temperature, acidified with 1 *N* hydrochloric acid, and filtered. Recrystallization of the precipitate from methanol gave 1.66 g. (32%) *N*-phenyl-3-methoxyphthalimide (IV), m.p. 185-187°, reported (5) 188.5-190°. The product did not depress the melting point of authentic IV. The product and authentic IV gave identical ir spectra (potassium bromide): 3325, 1705, 1480, 1380, 1282, 1045, and 750 cm^{-1}. The nmr spectrum (deuteriochloroform) showed a methoxy signal at δ 4.08.

Treatment of IIIa with Sodium Methoxide.

To a solution of 0.03 mole of sodium in 50 ml. of absolute methanol was added 0.02 mole of IIIa. The mixture was refluxed four hours, cooled, and acidified with 1 *N* hydrochloric acid, precipitating 4.8 g. (94%) of the starting material.

Treatment of V with Sodium Methoxide.

To a solution of 0.03 mole of sodium in 50 ml. of absolute methanol was added 0.02 mole of methyl 4-chlorophthalimidoacetate (V). The mixture was refluxed for four hours, producing a bright yellow, gelatinous mass. The mixture was cooled, acidified with 1 *N* hydrochloric acid, and filtered. Recrystallization of the precipitate from methanol gave 0.1 g. (2%) of yellow needles, m.p. 250° (dec.), uv λ max (95% ethanol) 345-346 nm, λ max (0.1 *N* NaOH) 380 nm.

Anal. Calcd. for $C_{11}H_8ClNO_4$: C, 52.09; H, 3.18; Cl, 13.98; N, 5.52. Found: C, 51.92; H, 3.48; Cl, 14.27; N, 5.51.

REFERENCES

(1) The authors gratefully acknowledge financial support of this work by The Robert A. Welch Foundation, through Research Grant No. M-101.

(2) Most recent paper in this series: F. C. Lee and L. R. Caswell, *J. Heterocyclic Chem.*, 8, 831 (1971).

(3) To whom correspondence should be addressed.

(4) Abstracted in part from the M.S. Thesis of L. I. S., now Mrs. Lily Fang.

(5) L. R. Caswell and T. L. Kao, *J. Heterocyclic Chem.*, 3, 333 (1966).

(6) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Second Edition, Allyn and Bacon, Boston, 1966, pp. 828-831.

(7) L. R. Caswell and P. C. Atkinson, *J. Org. Chem.*, 29, 3151 (1964).

(8) G. Marino, *Ric. Sci.*, 30, 2094 (1960).

(9) Melting points were determined with an Electrothermal melting point apparatus and are not corrected. Microanalyses were done by Atlantic Microlab, Inc., Atlanta, Georgia, or by PCR, Inc., Gainesville, Florida. Uv absorption spectra were determined with a Cary 15 spectrophotometer, ir absorption spectra with a Perkin-Elmer 225 grating spectrophotometer, and nuclear magnetic resonance spectra with a Varian A-60A nmr spectrometer.

(10) L. R. Caswell and E. D. Martinez, *J. Chem. Eng. Data*, 13, 286 (1968).

(11) L. R. Caswell and R. D. Campbell, *J. Org. Chem.*, 26, 4175 (1961).

(12) G. J. Marriott and R. Robinson, *J. Chem. Soc.*, 134 (1939).