LITHIATION OF 2-FLUORONAPHTHALENE

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SUMMARY

The lithiation of 2-fluoronaphthalene in tetrahydrofuran (THF) has been carried out using n-butyllithium. Carboxylation of the lithiated fluoronaphthalene yields a mixture of 2-fluoro-1-naphthoic acid (54%) and 2-fluoro-3-naphthoic acid (46%) The use of tert-butyllithium changes the product ratio toward 3-lithiation.

INTRODUCTION

In the course of our research in another area, we have experienced a need for a supply of the hitherto unreported 2-fluoro-3-naphthoic acid. We planned to obtain this material by carboxylation of 3-lithio-2-fluoronaphthalene but we found no literature reports of the preparation of this material. We describe here the results of our studies of the lithiation of 2-fluoronaphthalene.

Lithiation of fluorobenzene at low temperatures followed by carboxylation produces 2-fluorobenzoic acid in 60% yield[1]. More recently a wide variety of poly-fluorinated benzenes have been converted to their lithioderivatives[2]. The facility of removal of an *ortho*-hydrogen as a proton is attributed to the pronounced electro-negativity of the fluorine atom.

Lithiation of naphthalene derivatives has been studied only to a much lesser extent. Gilman and coworkers carried out the lithiation of 2-naphthol and some 2-alkoxynaphthalenes with n-butyllithium and observed formation of only the 3-acid upon carboxylation[3,4]. Graybill and Shirley[5] observed that lithiation of 1-methoxy-naphthalene by n-butyllithium produced major amounts of 1-methoxy-2-naphthoic acid upon carboxylation (83%), but some 1-methoxy-8-naphthoic acid (17%) was also isolated. Lithiation of 1,7-dimethoxynaphthalene has also been described[6].

Some halonaphthalenes have also been used as substrates in lithiation reactions. The lithiation of 1-fluoronaphthalene using n-butyllithium in THF at −55° has been carried out by Gilman and Soddy[1] who isolated a 30% yield of 1-fluoro-2-
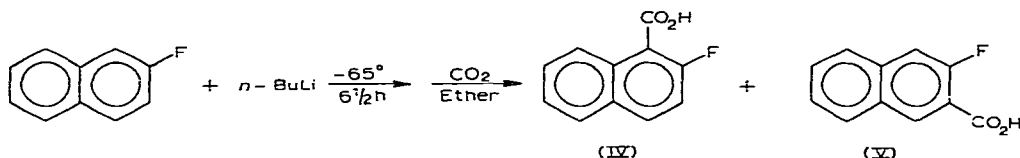

(I)　　　　(II)　　　　(III)

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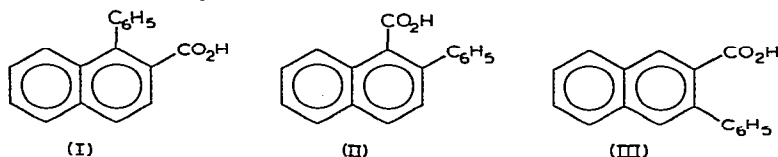
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naphthoic acid after carboxylation in ether. Huisgen and Rist have isolated the phenylnaphthoic acids (I)–(III) after treating either 1-fluoro- or 2-fluoronaphthalene with phenyllithium at 18° or 35°. Under these conditions, elimination to form 1,2- and 2,3-"naphthalyne" occurs[7]. Related studies of naphthalyne formation and reactivity using all four 2-halonaphthalenes have been reported by Bunnett[9].

RESULTS AND DISCUSSION

From the above reports, it was evident that our lithiation should be conducted at low temperature in order to avoid naphthalyne formation. Treatment of 2-fluoronaphthalene in THF under argon at −65° with n-butyllithium in hexane yielded greater than 70% yield of a mixture of two acids after carboxylation. The total recovery of organic material, including unreacted 2-fluoronaphthalene, was greater than 95%. Repeated recrystallizations resulted in the separation of two acids which had melting points of 151–153° and 196.5–198°, respectively. Based on comparisons with a variety of known naphthoic acids, it was most reasonable to assign the 1-carboxylic acid structure to the lower melting isomer. Proton NMR shows a down-

field doublet [8.67 δ, J(H–F) 7 Hz] in the spectrum of the higher melting isomer, while no such doublet is present in the spectrum of the lower melting isomer. This one proton doublet is assigned to the 4-proton resonance in 2-fluoro-3-naphthoic acid (V) with *meta*-coupling to the fluorine and downfield chemical shift due to the adjacent carboxyl group. Finally, a series of chemical reactions which converted the higher melting acid to the known 3-nitro-2-fluoronaphthalene proved conclusively that the lower melting acid had structure (IV) and the higher melting isomer structure (V).

Quantitative estimate of the amount of (IV) and (V) so formed could be made from either the integration of the NMR spectrum using the area under the peak due to the 4-proton as a measure of the amount of (V) or from VPC analysis of the mixed esters formed by reaction of the mixed acids with ethereal diazomethane. Both analyses gave results which were in agreement for 54% (IV) and 46% (V).

We have performed several additional experiments in order to derive a rationale for these results. The 54/46 ratio of products stands in stark contrast to Gilman's results[3] with 2-methoxynaphthalene as substrate in which he found *only* the 2-methoxy-3-naphthoic acid. The absence of 1-carboxylic acid in Gilman's study can be attributed to a resonance influence of the methoxyl group which overrides the inherently equal inductive acidification of the 1- and 3-protons. It is obvious that the much stronger inductive effect of the fluorine substituent is not so dominated by any mesomeric influence of fluorine, otherwise electron polarization in the 1-carbon–hydrogen bond would have greatly decreased the acidity of this proton causing the 1-acid to be a minor product. Resonance effects on this metallation reaction can thus be labeled unimportant.

Our 54/46 ratio differs somewhat from that suggested by Huisgen[8]. On the basis of the relative amounts of (I)–(III) isolated by reaction of fluoronaphthalene with phenyllithium at room temperature, they ascribed a 3/2 ratio to 1- to 3-lithiation. He did not have a direct measure of this ratio, however.

One would expect to observe some steric effect on the proton removal reaction which depended on the size of the attacking base, since the 1-proton is made somewhat less accessible due to *peri*-hydrogen interference. In support of this expectation, lithiation with tert-butyllithium in pentane/THF at −65° followed by carbonation produced a 55% yield of mixed acids with composition 39% (IV) and 61% (V). Larger organolithiums were not investigated. The smaller reagent methyllithium was not basic enough to produce any reaction with 2-fluoronaphthalene at −65°.

The question of why lithiation of naphthalene itself produces a 2.5/1 ratio (analysis by weight after separation) of 1- to 2-naphthoic acid was puzzling[10]. We repeated this reaction using n-BuLi in both hexane/THF and ether/hexane solvent mixtures at room temperature, and although the reaction was considerably slower (20% lithiation after 15 h), the product composition determined by NMR methods directly on the acid mixture was in fact 54% 1- and 46% 2-naphthoic acid. Thus, there is absolutely no positionally selective acidification effect by fluorine.

The behavior of the lithiofluoronaphthalenes at temperatures above −65° was investigated briefly. Direct lithiation using n-butyllithium at −10° for 1 h followed by aqueous quenching yielded—in addition to major amounts of unreacted fluoronaphthalene—n-butylnaphthalene,·an isomeric mixture of monofluorobinaphthyls ($M^+ = m/e$ 272) and some dibenzobiphenylene ($M^+ = m/e$ 252). Generation of the lithiofluoronaphthalenes at −65° and warming to −30° resulted in an exothermic reaction which raised the temperature of the mixture rapidly to −15°. Immediate cooling to −30° and quenching with Dry Ice yielded only small amounts of acidic materials [(IV) and (V) ($M^+ = m/e$ 190), isomers of (VI) ($M^+ = m/e$ 296), and isomers

(VI)   (VII)
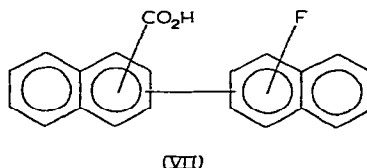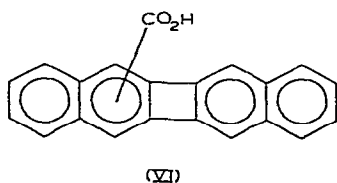
of (VII) ($M^+ = m/e$ 316)], major amounts of tribenzotriphenylene isomers ($M^+ = m/e$ 378) and monofluorobinaphthyls ($M^+ = m/e$ 272) and small amounts of dibenzobiphenylene ($M^+ = m/e$ 252) and n-butylnaphthalene*. All of these products result from reactions of the isomeric naphthalynes and all have precedent in benzyne and naphthalyne chemistry. Thus, at temperatures above −35°, we have established that one cannot hope to observe reactions of *ortho*-lithiofluoronaphthalenes uncomplicated by reactions of naphthalyne.

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* NMR and IR spectra were in agreement with those postulations but no concerted efforts were made to completely separate the isomeric mixtures encountered.

EXPERIMENTAL

Materials

2-Fluoronaphthalene was obtained from Aldrich Chemical Company, and was recrystallized from ethanol before use. Tetrahydrofuran (THF) was dried according to the procedure of Gilman and Soddy[1] before use. n-Butyllithium was obtained from Foote Mineral Company as a 1.6 M solution in hexane, and tert-butyllithium was also obtained from Foote Mineral Company as a 1.24 M solution in pentane.

General procedures

Mass spectra were obtained on an Atlas CH4 mass spectrometer. The NMR spectra were obtained on a Varian A60 Spectrometer in dimethylacetamide as solvent and with tetramethylsilane as internal reference. IR spectra were obtained on a Perkin–Elmer Model 21 spectrometer as KBr pellets. Analyses were obtained from Chemalytics, Inc., Tempe, Arizona. Melting points were obtained on a Thomas, Kofler micro hot stage.

Lithiation using n-butyllithium

To a three necked round bottomed flask, under Ar, containing 22.1 g of 2-fluoronaphthalene in 150 ml of THF was added at −60°, 96 ml of a solution of n-butyllithium in hexane (1.6 M). The mixture was stirred at approximately −60° for $6\frac{1}{2}$ h. It was then poured into a slurry of Dry Ice in ether and allowed to stand overnight. The mixture was then extracted with aq. KOH and the basic extracts acidified with HCl to yield a white solid in approximately 70% yield. Attempted recrystallization from water yielded a number of fractions. Purification of several fractions resulted in the isolation of two products. The products obtained were identified as 2-fluoro-1-naphthoic acid (IV) and 2-fluoro-3-naphthoic acid (V). Recrystallization of (IV) from ethanol gave colorless needles m.p. 151–153°. The NMR in dimethylacetamide showed a multiplet at 7.33–7.80 δ (3H), multiplet at 7.97–8.33 δ (3H), and a broad singlet at approximately 12.5 δ. The mass spectrum included peaks with *m/e* 190, 173, 145, and 125 (Found: C, 69.50; H, 3.59. $C_{11}H_7FO_2$ calcd.: C, 69.47; H, 3.71%.) Recrystallization of (V) from ethanol gave colorless needles m.p. 196.5–198°. The NMR in dimethylacetamide showed a multiplet at 7.40–8.33 δ (5H), doublet at 8.67 δ (1H), [J(H–F)=7 Hz], and a broad singlet at approximately 12.5 δ. The mass spectrum included peaks with *m/e* 190 (base), 173, 145, and 125 (Found: C, 69.54; H, 3.59. $C_{11}H_7FO_2$ calcd.: C, 69.47; H, 3.71%.)

Lithiation of 2-fluoronaphthalene using tert-butyllithium

The procedure was the same as described above using a 1.24 M solution of tert-butyllithium in pentane.

Lithiation of naphthalene

To 50 ml of THF containing 5 g of naphthalene under argon was added 20 ml of a solution of n-butyllithium in hexane. The mixture was stirred at room temperature for 15 h, then poured into a slurry of Dry Ice in ether and allowed to stand overnight. Usual workup resulted in isolation of 3.0 g of solid acid, analyzed as 54% 1- and 46% 2-naphthoic acid by the technique described below.

Product analysis procedure

The mixtures of acidic products encountered in this work were analyzed by proton NMR using dimethylacetamide as solvent. The spectrum of 2-fluoro-3-naphthoic acid showed a doublet at 520 Hz from TMS which was separate from the remainder of the spectrum. Simple integration of the spectrum was used a measure of the amount of (V) present.

Esterification of the acid mixture with an excess of diazomethane in ether gave a mixture of esters which were injected into the gas chromatograph and the quantitative results obtained were in agreement with those from the above NMR measurements on the free acids. Integration of the NMR spectrum of the esters also gave the same results.

The mixture of naphthoic acids from the lithiation of naphthalene was also analyzed by NMR in dimethylacetamide. The spectrum of 1-naphthoic acid contained a one proton doublet of doublets at 9.17 δ which was separate from the rest of the absorption, and the spectrum of 2-naphthoic acid contained a one proton singlet at 8.77 δ which was also separate from the rest of the absorption. In the mixture of the acids, these protons were separate from each other and the rest of the spectrum, and integration and comparison of the areas of these two protons yielded the relative amounts of the products.

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