An Improved Route for the Synthesis of 1-Amino-2-methylnaphthalene[1]

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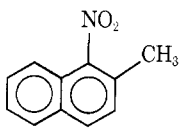
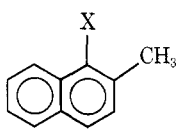
When a chemist wishes to prepare a primary aromatic amine the classic approach has been to nitrate the nucleus in question and then to reduce the nitro compound thus obtained. In this paper we show that if 1-amino-2-methylnaphthalene is the desired compound, an alternate approach is preferable. 1-Amino-2-methylnaphthalene was needed as a precursor to several disubstituted naphthalenes of interest in the synthesis of compounds desired for testing in the cancer program.

In the first place, nitration is a reaction which often proceeds with less selectivity than many other electrophilic aromatic substitution reactions. This means that often the nitration product is a mixture of isomers. Frequently the yield of crude nitration product is cited and also the melting point of the desired isomer but too often there is no indication of what yield of pure isomer is to be expected. Furthermore, the products of nitration are quite sensitive to the nitrating species.[3] In the present case, nitration of 2-methylnaphthalene near 0 °C has been reported[4] to yield 58% of 1-nitro-2-methylnaphthalene (1) (plus 42% of an unknown mixture of



1 (X = NO_2)



2 (X = Br)
3 (X = COOH)
4 (X = NH_2)

other nitro-2-methylnaphthalenes) and to yield 1, mp 80–81 °C, in unspecified yield from 60% of solid nitro compound.[5] That even the 58% of 1-nitro-2-methylnaphthalene was not pure is indicated by the fact that monobromination of the 1-amino-2-methylnaphthalene produced by reduction of 1 needed several recrystallizations to afford a pure sample of 1-amino-4-bromo-2-methylnaphthalene in 31% yield[6] (some impurities may have resulted from the bromination procedure). In our experience with the nitration of 2-methylnaphthalene, we have found that the yield varies from run to run and that recrystallization to obtain pure 1 is tedious and accompanied by large diminutions in yield. Accordingly we have developed the method described below.

Bromination[7] of 2-methylnaphthalene affords an 88% yield of almost pure 1-bromo-2-methylnaphthalene (2). This material is converted via the Grignard reagent into 2-methyl-1-naphthoic acid (3), shown to be almost pure by subjecting to acid-catalyzed esterification. Acids other than 3 are esterified and hence easily separated from the sterically hindered acid, 3, which is obtained pure in 77% overall yield from 2. Finally, 3 is converted into 1-amino-2-methylnaphthalene (4) in high yield (see Experimental Section) by treating a sulfuric acid solution (90.8% by weight) with sodium azide. Because 4 is sensitive to air it is best converted to the *N*-formyl derivative, 5, if it is to be brominated.

The extreme sensitivity to sulfuric acid strength of the Schmidt reaction in converting 3 to 4 is noteworthy. If 96% sulfuric acid was used, the amine formed was sulfonated and only water-soluble products were obtained. If 90% sulfuric acid (possibly weaker as no titration was performed) was used, mostly unchanged 3 was recovered. The best yield was obtained with 90.8% sulfuric acid by weight, but no other reactions in which titrated H_2SO_4 was used were studied.

We believe that the route we have developed is preferable to the nitration route because higher yields of purer product may be obtained even though an extra step is involved. It is noteworthy that separation of the desired isomer is accomplished by taking advantage of chemical reactivity (the inability of the desired acid, 3, to be esterified) rather than having to rely on a physical method, i.e., recrystallization, for purification of 1.

Experimental Section

1-Bromo-2-methylnaphthalene (2). A solution of 320 g of bromine in 180 ml of acetic acid was added during 3 h to a well-stirred solution of 284 g of 2-methylnaphthalene[8] in 375 ml of glacial acetic acid containing 10 g of $AlCl_3$ and 1 ml of pyridine (the rate of bromination is less if the pyridine is omitted). After 2 more h the mixture was poured into 1.5 l. of water and the product taken into 1:1 ether–benzene. After a conventional workup (which included a wash with $NaHSO_3$) the solvent was removed on a rotary evaporator and the residue was vacuum distilled through a short column to yield 409 g (92%) of 2, bp 148–149 °C (8 mm). In other runs when material having a slightly larger distilling range was collected some further purification procedures were applied prior to attempting to prepare the Grignard reagent. One procedure involved boiling with a small amount of aqueous alcoholic KOH followed by washing the solvent-free product thus obtained with 75% H_2SO_4 until no color was observed in the H_2SO_4 layer. Whether or not this purification is advisable could be found out by treating a small amount of crude 2 with alcoholic $AgNO_3$. If no precipitate of AgBr was formed no side-chain bromination had occurred and then alkaline treatment is unnecessary. The other procedure involved shaking a chloroform solution of crude 2 with portions of 75% H_2SO_4 as often as color was formed in the H_2SO_4 layer. The product was then recovered and distilled. Overall yields of 83–88% of pure 2 suitable for facile conversion to Grignard reagent were the rule.

2-Methyl-1-naphthoic Acid (3). In a typical reaction, a solution of 155 g of 2 in 400 ml of ether containing 2 ml of ethylene dibromide was added to a stirred mixture of 20 g of Mg and 180 ml of ether (previously activated by treatment with a small amount of ethylene dibromide[9]) during 2 h. As soon as a trace of oily layer was apparent sufficient benzene was added to dissolve the oily layer. In all about 200 ml of benzene was needed. After being held at reflux for 1 h the cooled Grignard reagent was poured rapidly on crushed solid CO_2 (a large but unmeasured excess) in a 4-l. beaker. A conventional workup, which included extraction of the acid by 15% KOH solution, yielded crude 3 which was promptly treated with ethanol, benzene, and an acid catalyst at reflux under a phase-separating head. After several hours at reflux (the amount of acid esterified by this treatment is so small that a second layer is not seen in the head) the pure acid is recovered by a conventional workup as an almost colorless solid, mp 125–127 °C (lit.[10] mp 126–127 °C), in 77–80% overall yield from 2. The small amount of ester recovered from the neutral fraction had two components [NMR CH_3 peaks when methanol was used for esterification at 1.18 ppm (minor component) and 1.23 ppm].

1-Amino-2-methylnaphthalene (4). Our best results were obtained by adding 7.8 ml of water to 100 ml of commercial concentrated H_2SO_4 (97% by titration). To a stirred solution of 25 g of 3 in 200 ml of 90.8% H_2SO_4 held at 0–5 °C was added 13 g of NaN_3 in small portions during 2 h. After another 3 h the yellow-orange solution was poured on 500 ml of ice and water. The mixture was made basic by the addition of 900 ml of 40% NaOH. The amine was taken into ether–benzene and after the usual workup was distilled to yield 16.2 g (77%) of pure 4, bp 150 °C (4 mm) [lit.[11] bp 141–143 °C (5 mm)]. In smaller runs (5 g of 3) higher yields (80–85%) were occasionally obtained and on a larger run (65 g) the yield dropped to 70%. The amine darkens rapidly on standing and should be used as soon as convenient.

Registry No.—2, 2586-62-1; 3, 1575-96-8; 4, 2246-44-8; 2-methylnaphthalene, 91-57-6.

References and Notes

(1) This work was supported by Grant CA-07394 and by Contract CP 43248 of the National Cancer Institute.
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(7) An improved bromination in acetic acid containing a small amount of pyridine is described in the Ph.D. Thesis of A. I. Kosak, The Ohio State University, 1948, and in the Experimental Section.
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A Convenient Synthesis of 1,2-Naphthalic Anhydride[1]

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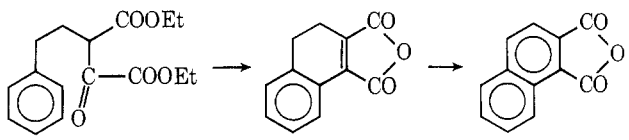
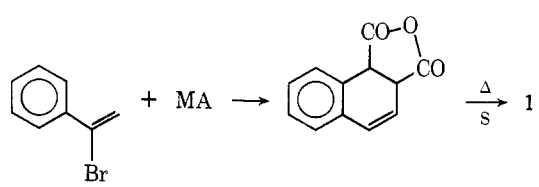
1,2-Naphthalic anhydride (**1**) has long been used for the elaboration of compounds in the benz[*a*]anthracene series.[3] An early synthesis of **1** involved cyclization of ethyl 3-carboethoxy-2-oxo-5-phenylpentanoate (**2**) to 3,4-dihydronaphthalene-1,2-dicarboxylic acid anhydride (**3**) followed by aromatization by heating with sulfur.[4] Later, 1,2-dihydronaphthalene-1,2-dicarboxylic anhydride (**4**), together with a small amount of **1**, were prepared by heating α-bromostyrene (**5**) with maleic anhydride[5] but no developmental work on this route to **1** has been reported. An attempt to convert β-bromostyrene to **4** by heating with maleic anhydride failed.[6] We have tried to use α-chlorostyrene instead of **5** but obtained none of the desired **4**. In this note we record our observations on an improved preparation of **1** by the styrene route.



2 **3** **1**

We have converted styrene dibromide to **5**, by using phase transfer catalysis.[7] In the final dehydrogenation of **4** by heating with sulfur, we have found that the **1** produced always contains some sulfur compound which is not removed by recrystallization. However, by boiling **1** in aqueous alkali, acidification, and cyclization to the anhydride pure sulfur-free **1** can be obtained in satisfactory overall yield.



5 **4**

In our opinion it is much easier to prepare quantities of **1** by the styrene route than by the earlier cyclization of the keto diester[4] as it is relatively simple to carry out the reactions involved on a large (2–3 mol) scale.

Experimental Section

α-Bromostyrene (5). In the best experiment, a solution of 336 g of bromine in 250 ml of $CHCl_3$ was added to a cooled (ca. 5 °C) solution of 208 g of freshly distilled styrene in 250 ml of $CHCl_3$. The temperature was not allowed to rise above 15 °C but cooling to 5 °C near the end is not advisable because the product will crystallize prematurely. After all of the bromine was added the reaction mixture was allowed to stand at room temperature for 1 h. The solvent was then removed to constant weight on a rotary evaporator. The yield of styrene dibromide is practically quantitative.

In the best of many runs, a solution of the crude styrene dibromide thus obtained in 800 ml of benzene was added fairly rapidly to a well-stirred mixture at 70 °C of 528 g of KOH, 800 ml of water, and 10 g of Aliquat 336.[8] The mixture was held at reflux for 3 h.[9] After cooling, the benzene layer was washed with water and saturated salt solution, passed through a cone of anhydrous $MgSO_4$, and fractionally distilled to afford 301 g (82.7%) of **5**, bp 80–83 °C (10 mm). In other similar runs which varied in detail yields of 52–79% were obtained. The yield is somewhat dependent on the skill of the operator in conducting a rapid distillation. If the distillation is conducted too slowly thermal decomposition occurs and the yield is lower. The use of a hot salt bath and a free flame to hasten distillation is recommended.[10]

1,2-Naphthalic Anhydride (1). In the best of many runs, a solution of 408 g of **5** and 326 g of maleic anhydride in 1.5 l. of xylene was refluxed for 48 h (to ensure escape of most of the HBr formed). The solvent was then distilled and the residue was rapidly vacuum distilled to yield crude **4**, bp 150–165 °C (1 mm), which was immediately placed in a Claisen flask with 71 g of sulfur. The mixture was heated rapidly to 230–235 °C with a salt bath and held at this temperature for 1 h, then at 250 °C for 1 h. Rapid vacuum distillation afforded 300 g (69%) of crude **1**, mp in the 160–164 °C range. The yields in this step varied from 63 to 75% (small-scale run). This product contains sulfur-containing impurities and cannot be effectively purified by crystallization. The best method of purification involved heating at reflux for 4 h 131.5 g of crude **1** with excess 20% NaOH. On acidification of the filtered solution followed by heating of the acid with 1 l. of $(Ac)_2O$, there was obtained 116.9 g (89%) of **1** in three crops. The melting points lay in the 165–167 °C range and this material was suitable for further work. No sulfur was present as shown by the absence of *m/e* over 198.

Registry No.—**1**, 5343-99-7; **4**, 60224-29-5; **5**, 98-81-7; styrene, 100-42-5; styrene dibromide, 93-52-7; maleic anhydride, 108-31-6.

References and Notes

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(2) Postdoctoral Research Associate.
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(9) Refluxing for longer times results in the formation of larger amounts of phenylacetylene, bp below 75 °C (10 mm).
(10) The technique is described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, pp 23, 35.

The Chemistry of a Ketene–Sulfur Dioxide Adduct. 3. Reactions with Azines

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The cycloadditions of imines with ketene–sulfur dioxide adduct (**1**)[1b,c] to give substituted thiazolidin-4-one 1,1-dioxides was described in earlier publications,[1a,b] and extended by Kagan et al.[2] to substituted ketenes. More recently, Bellus reported that ketenes containing carbanion stabilizing substituents, generated in situ in the presence of sulfur dioxide,