from standard commercial sources, variously labeled forms of [^{14}C]oxaloacetic acid are readily obtained from correspondingly labeled [^{14}C]-aspartic acid, a commonly offered commercial product (cf. A. Goldstone and E. Adams, *J. Biol. Chem.*, **240**, 2077 (1965)).
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A Convenient Synthesis of 3- and 4-Methylphthalonitrile

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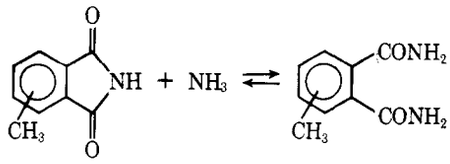
Recent interest in more soluble derivatives of N-donor chelating ligands, such as phthalocyanine[1,2] and 1,3-bis(2-pyridylimino)isoindoline,[3,4] made desirable a facile synthesis for precursor alkyl-substituted phthalonitriles. Although 3- and 4-methylphthalonitrile were first prepared many years ago, the multi-step synthesis is time consuming and deficient in overall yield.[5-8] More recently, alternate syntheses for alkyl-substituted phthalonitriles have been reported, but they rely upon less readily available starting materials.[9-11] We report here a convenient high yield synthesis of 3- and 4-methylphthalonitrile from the commercially available phthalic anhydrides. 3- and 4-alkylphthalic anhydrides are particularly suitable starting materials because alkyl-substituted phthalic anhydrides are obtainable from dehydrogenation of Diels–Alder adducts of maleic anhydride and the appropriately substituted butadienes.[12]

Results and Discussion

Although unsubstituted phthalic anhydride may be readily converted to phthalonitrile via phthalimide and phthalamide intermediates, this chemical reaction sequence fails when applied to the synthesis of alkyl-substituted phthalonitriles. 3- and 4-methylphthalic anhydride **1** are readily converted to the corresponding imide **2** in high yield. However, unlike phthalimide itself, which reacts with ammonium hydroxide to form phthalamide in good yield, 3- and 4-methylphthalimide **2** react with ammonium hydroxide under identical conditions to form a water-soluble product characterized as the ammonium half-salt of the acid amide **4** (probably a mixture of the the two possible positional isomers). The infrared and elemental analyses are consistent with the presence of carboxylate and amide groups. Treatment of the salt **4** with thionyl chloride or heat resulted in reconversion to the starting imide **2**; treatment of salt **4** with dilute acid afforded the corresponding phthalic acid **5**.

Conversion of 3- or 4-methylphthalimide **2** to the diamide **3** was possible upon treatment of the imide with dry ammonia; up to 80% conversion was obtained and unreacted imide could be recycled. The difference in reactivity between unsubstituted phthalimide and 3- or 4-methylphthalimide **2** may be associated with the imide–amide equilibrium (eq 1), which is



(1)

apparently less favorable for 3- or 4-methylphthalamide than it is for unsubstituted phthalamide.

3-Methylphthalamide (**3**) was more easily converted to the nitrile **6** than was the 4-methyl derivative. With acetic anhydride the yield of 3-methylphthalonitrile was only 15%, but with $SOCl_2$/DMF at 0 or −12 °C the yield was as high as 80%. With acetic anhydride the yield of 4-methylphthalonitrile was considerably less than 15% and with $SOCl_2$/DMF at 0 °C the yield was still negligible (in the latter case the imide was the only major product observed). However, reducing the temperature of the $SOCl_2$/DMF reaction to −12 °C or using reverse addition resulted in yields of 4-methylphthalonitrile as high as 84%. The beneficial effect of lower temperatures on the $SOCl_2$/DMF dehydration of aromatic amides was reported earlier by Thurman.[13]

The convenient three-step sequence presented here allowed formation of 3-methylphthalonitrile in 60% and 4-methylphthalonitrile in 62% overall yield from commercially available starting materials.

Experimental Section

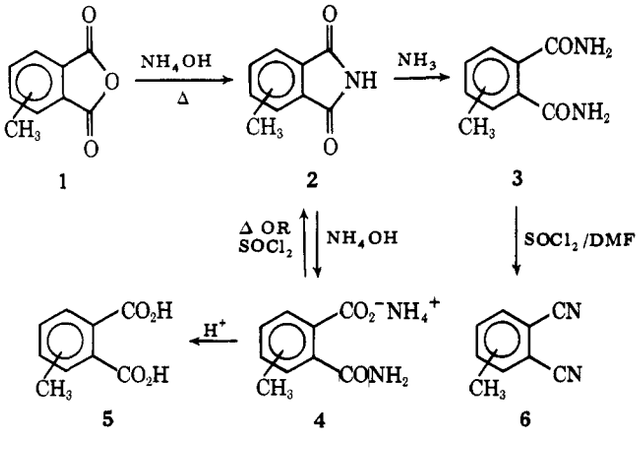
3- and 4-methylphthalic anhydride were obtained from Eastman Chemicals and used as obtained. Infrared spectra were recorded from KBr pellets on a Perkin-Elmer Model 457 spectrophotometer; only pertinent absorption bands are reported. NMR spectra were recorded where solubility permitted with tetramethylsilane as an internal standard. Melting points are reported uncorrected. Microanalyses were performed by Central Laboratory Services of the Ford Motor Company.

3-Methylphthalimide. The imide was prepared from 3-methylphthalic anhydride according to the general procedure of Noyes and Potter.[14] The 3-methylphthalimide was conveniently purified by Soxhlet extraction with benzene and was obtained in 98% yield as white crystals, mp 186–187 °C (lit.[8] 189–190 °C).

4-Methylphthalimide. This imide was obtained by the same method as white crystals in 93% yield, mp 195–196 °C (lit.[6] 196 °C).

Reaction of 3-Methylphthalimide with Ammonium Hydroxide. A flask was charged with 0.22 g of 3-methylphthalimide, 5 mL of ethanol, and 8 mL of aqueous ammonia. The mixture was stirred at 24 °C for 40 h. After the solvent was evaporated under a stream of N_2, the residue was recrystalized from methanol–ethyl acetate to yield

Scheme I



0.10 g of off-white crystalline powder: mp 137–139 °C; IR (KBr) 3380 (m), 3170 (m), 1650 (s), 1590 (m-s), 1560 (s), 1468 (m), 1440 (m), 1390 (s) cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 53.73; H, 6.64; N, 12.92. Material obtained from other runs of this reaction likewise failed to give good C, H, and N analyses; attempts at further purification of the salt resulted in decomposition.

Reaction of 4-Methylphthalimide with Ammonium Hydroxide. When 4-methylphthalimide was treated with NH_4OH as described above, an off-white powder was obtained. Recrystallization of the powder from water–ethanol afforded white crystals: mp 172–173 °C (melting point was not consistent from batch to batch); IR (KBr) 3420 (m-s), 3180 (m-s), 1710 (w), 1670 (m), 1620 (m-s), 1578 (m), 1538 (m-s), 1410 (m-s), 1390 (m-s) cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.84; H, 6.15; N, 14.29.

A sample of the salt was treated with 10% hydrochloric acid. After the solvent had evaporated the residue was extracted with ethyl acetate. Addition of heptane to the extract induced crystallization of 4-methylphthalic acid: mp 156–157 °C (lit.[7] 152 °C); IR (KBr) ν_{CO} 1690 (s, br) cm^{-1}.

To a slurry of the salt (1.0 g) in 12 mL of DMF which was cooled to ca. −10 °C was added dropwise 1.7 mL of thionyl chloride. After the addition was complete, the temperature was allowed to rise to 24 °C and stirring was continued for 16 h. The reaction mixture was poured over 50 mL of ice and then filtered to collect 0.82 g (90%) of a white powder, spectroscopically identical with an authentic sample of 4-methylphthalimide.

A 50-mg sample of the salt was heated in an evacuated glass vessel for 15 min at 196 °C. Recrystallization of the cool melt from benzene–heptane afforded 33 mg (79%) of white powder: mp 194–195.5 °C (lit.[6] 196 °C), spectroscopically identical with 4-methylphthamide.

3-Methylphthalamide. A 3-oz glass pressure vessel was charged with 4.01 g (24.9 mmol) of 3-methylphthalimide and 4 mL of dry DMF. The suspension was cooled to 0 °C and the ammonia gas was bubbled in for 30 min. The vessel was pressurized to 50 psi and then heated for 8 h at 45 °C. After cooling to room temperature the pressure was carefully released. Acetonitrile (20 mL) was added with stirring and the mixture was suction filtered. After vacuum drying (70 °C) 3.38 g of 3-methylphthalamide (76% yield) was obtained as a white powder: mp 225 °C; IR (KBr) 3420 (m-s), 3330 (m), 3200 (m), 1680 (m), 1655 (s), 1610 (m-s), 1582 (w-m) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.34; H, 5.72; N, 15.75.

3-Methylphthalimide (1.07 g) was recovered from the filtrate and could be recycled.

4-Methylphthalamide. A 3-oz glass pressure vessel was charged with 4.01 g of 4-methylphthalimide and 40 mL of absolute ethanol. After the mixture was cooled to 0 °C, ammonia was bubbled into the suspension for 30 min. The reaction mixture was pressurized with ammonia until a pressure of 50 psi was maintained, and the mixture was then heated for 18 h at 50 °C. After cooling to room temperature, the pressure was carefully released and the mixture was filtered. Pure 4-methylphthalamide, 3.56 g (80% yield), was obtained: mp 188 °C (lit.[7] 188 °C); IR (KBr) 3435 (m-s), 3235 (m), 3200 (m), 1690 (m), 1655 (s), 1630 (sh), 1605 (m-s), 1582 (w-m) cm^{-1}.

3-Methylphthalonitrile. Method A. A flask was charged with 1.00 g of 3-methylphthalamide, 15 mL of dry DMF, and a magnetic stir bar, and was capped with a rubber septum and cooled to 0 °C (ice bath). Thionyl chloride (1.49 g) was added with stirring over a 30-min period (via syringe). The reaction mixture was allowed to slowly warm to room temperature and was then poured over 80 g of ice. The water-insoluble product was collected by filtration, washed with water, and dried. The yield of 3-methylphthalonitrile was 0.638 g (80%): mp 143 °C (lit.[8] 143 °C); IR (KBr) ν_{CN} 2230 cm^{-1}.

Method B. A suspension of 3.77 g (21.2 mmol) of 3-methylphthalamide in 20 mL of dry DMF was added to a solution of 3.9 mL (53 mmol) of thionyl chloride in 9 mL of DMF which had been cooled to 0 °C. The addition was made over a 30-min period; after an additional 30 min, the reaction mixture was poured over ice (150 g). The product was collected by filtration and dried to afford 1.18 g (39%) of the dinitrile.

4-Methylphthalonitrile. Method A. A flask was similarly charged with 1.00 g of 4-methylphthalamide, 15 mL of dry DMF, and a magnetic stir bar, and was capped with a rubber septum and cooled to −12 °C (NaCl–ice bath). Thionyl chloride (1.48 g) was added (via syringe) with stirring over a 30-min period. The reaction mixture was allowed to warm to room temperature and stirring was continued for ca. 16 h. The reaction mixture was poured over 83 g of ice and the insoluble product was collected by filtration, washed with water, and dried. The yield of 4-methylphthalonitrile was 0.39 g (48%): mp 120 °C (lit.[6] 120 °C); IR (KBr) ν_{CN} 2255 cm^{-1}.

Method B. A suspension of 3.90 g (21.9 mmol) of 4-methylphthalamide in 20 mL of dry DMF was added to a solution of 4.0 mL (55 mmol) of thionyl chloride in 20 mL of DMF which had been cooled to 0 °C. The addition was carried out over a 20-min period, after which the mixture was allowed to warm to room temperature. The reaction mixture was poured over ice and the product collected by filtration. A white powder (mp 122 °C) was obtained in 84% yield (2.62 g).

Registry No.—3-methyl-**2**, 7251-82-3; 4-methyl-**2**, 40314-06-5; 3-methyl-**3**, 63089-46-3; 4-methyl-**3**, 63089-47-4; 3-methyl-**4**, 63089-48-5; 4-methyl-**4**, 63089-49-6; 4-methyl-**5**, 4316-23-8; 3-methyl-**6**, 36715-97-6; 4-methyl-**6**, 63089-50-9.

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The Bimolecular Elimination of *trans*-2-Methylcycloocytl Tosylate. A Reinvestigation

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Our continuing interest in the synthetically useful reactions of eight-membered rings[1a–c] has recently led us to reinvestigate the elimination reaction of *trans*-2-methylcycloocytl tosylate. In 1966, Brown and Klimisch published preliminary results[2] on that reaction as part of a study of E2 eliminations in a series of *trans*-2-methylcycloalkyl tosylates, using potassium *tert*-butoxide in *tert*-butyl alcohol. For the five-, six-, and seven-membered rings, they obtained a 99:1 ratio of 3-methylcycloalkene to the 1-methyl isomer. However, this expected selectivity (based on the well-documented stereoelectronic requirement for an anti-periplanar transition state

Table I

Conditions[a]	cis-1-Methylcyclooctene	*cis*-3-Methylcyclooctene
Literature[2]	1	1
50 °C, 3 h, KO-*t*-Bu, *t*-BuOH	2	1
50 °C, 3 h, Na_2CO_3, *t*-BuOh	2.5	1
25 °C, 30 min, KO-*t*-Bu, Me_2SO	1	23

[a] Both alkenes are stable to these reaction conditions.