Syntheses of 9-(Trifluoromethyl)- and 10-(Trifluoromethyl)-7,12-dimethylbenz[a]anthracenes[1]

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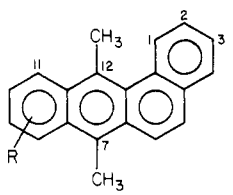
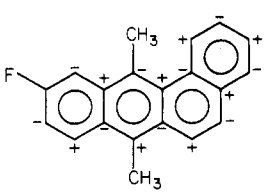
4,4-Dimethyl-2-(2-lithio-4-(trifluoromethyl)phenyl)-2-oxazoline reacted with 2- and 1-naphthaldehydes to afford, after hydrolysis, 3-(2-naphthyl)-5-(trifluoromethyl)phthalide (**6**) and 3-(1-naphthyl)-5-(trifluoromethyl)phthalide (**7**), respectively. Hydriodic acid reduction of these phthalides yielded 2-(2-naphthylmethyl)-4-(trifluoromethyl)benzoic acid (**8**) and 2-(1-naphthylmethyl)-4-(trifluoromethyl)benzoic acid (**9**), which were cyclized and oxidized to 9-(trifluoromethyl)-7,12-benz[a]anthraquinone (**10**) and 10-(trifluoromethyl)-7,12-benz[a]anthraquinone (**11**), respectively. Reaction of these quinones with methyllithium followed by stannous chloride–hydrochloric acid reduction of the resulting diols gave 9-(trifluoromethyl)-7,12-dimethylbenz[a]anthracene (**12**) and 10-(trifluoromethyl)-7,12-dimethylbenz[a]anthracene (**13**), respectively. In a different route, 2-(3-(trifluoromethyl)benzoyl)-1-naphthoic acid (**15**), prepared from *m*-(trifluoromethyl)phenylmagnesium bromide (**14**) and 1,2-naphthalic anhydride, was reacted with methylmagnesium bromide to obtain 2-[1-hydroxy-1-(3-(trifluoromethyl)phenyl)ethyl]-1-naphthoic acid lactone (**16**). Zinc–alkali reduction of **16** yielded 2-[1-(3-(trifluoromethyl)phenyl)ethyl]-1-naphthoic acid (**17**), the acid chloride of which afforded 1-acetyl-2-[1-(3-(trifluoromethyl)phenyl)ethyl]naphthalene (**18**) on treatment with lithium dimethylcuprate. Although 2-[(3-(trifluoromethyl)phenyl)hydroxymethyl]-1-naphthoic acid lactone (**19**), obtained by the reduction of **15** with triethylsilane, underwent a reductive ring closure to 9-(trifluoromethyl)benz[a]anthracene (**20**), attempted cyclization of **18** did not yield the anticipated **12**.

Tumor-initiating studies[3] on male rats have shown that the carcinogenic activity of 10-fluoro-7,12-dimethylbenz[a]anthracene (10-F-DMBA, **1**)[4] is greater than that of 7,12-dimethylbenz[a]anthracene (DMBA, **2**), which in turn is more potent than 9-F-DMBA (**3**).[4] In 10-F-DMBA the



1, R = 10-F
2, R = H
3, R = 9-F



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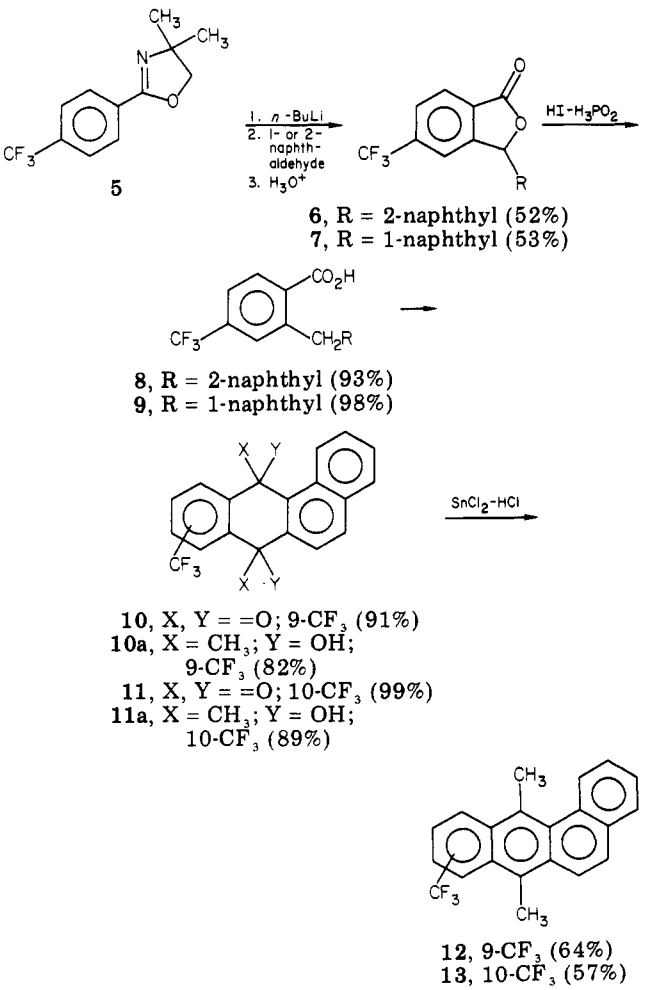
resonance property of an aromatic fluorine distributes positive and negative signs at the positions indicated in **4**. These signs are reversed in 9-F-DMBA. Metabolism leading to carcinogenic metabolites postulated by the diol epoxide theory[5] undoubtedly takes place in the angular ring. If one assumes that enzymic attack is electrophilic, then **1** is probably first attacked at the 4-position. The 4-position of **3** carries a positive sign, thereby accounting for its lower reactivity compared to that of either **1** or **2**.

In order to test the above reasoning, we decided to synthesize 9-CF_3-DMBA, **12**, and 10-CF_3-DMBA, **13**, so that their carcinogenic activity could be assessed. Since the CF_3 group is exclusively electron withdrawing, our explanation predicts that both 9- and 10-CF_3-DMBA's will be less active than DMBA.

Scheme I



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6, R = 2-naphthyl (52%)
7, R = 1-naphthyl (53%)

8, R = 2-naphthyl (93%)
9, R = 1-naphthyl (98%)

10, X, Y = =O; 9-CF_3 (91%)
10a, X = CH_3; Y = OH; 9-CF_3 (82%)
11, X, Y = =O; 10-CF_3 (99%)
11a, X = CH_3; Y = OH; 10-CF_3 (89%)

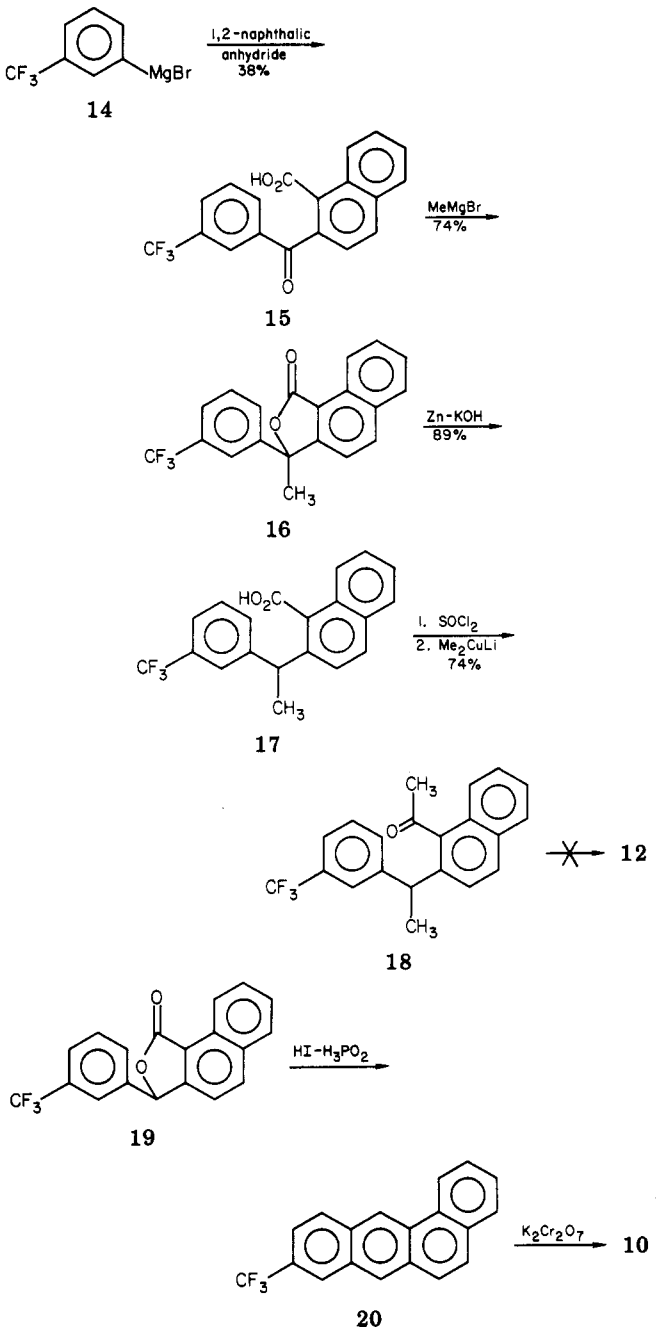
12, 9-CF_3 (64%)
13, 10-CF_3 (57%)

In tests involving 16 female outbred CD(SD) rats 4 μmol of 9- and 10-CF_3-DMBA was injected subcutaneously. By 7 months three rats had sarcomas from 9-CF_3-DMBA and none from 10-CF_3-DMBA. After 8 months there were eight rats with sarcoma from 9-CF_3-DMBA and none from 10-

(1) Research supported by a grant (CA 07394) from NIH.
(2) Postdoctoral research associate.
(3) Personal communication from Drs. J. A. Miller and E. C. Miller, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI.
(4) For syntheses of 9-F- and 10-F-DMBA's see: Newman, M. S.; Kannan, R. *J. Org. Chem.* **1979**, *44*, 3388.
(5) Jerina, D. M.; Thakker, D. R.; Yogi, H.; Levin, W.; Wood, A. W.; Conney, A. H. *Pure Appl. Chem.* **1978**, *50*, 1033. Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H. "Polycyclic Hydrocarbons and Cancer"; Academic Press: New York, 1978; Vol. 1, p 189.

0022-3263/83/1948-3246$01.50/0

Scheme II



CF_3-DMBA. The trioctanoin controls gave no sarcomas. These results mean that the interpretation of the carcinogenic activity of 9-F- and 10-F-DMBA given above is not as simply explained as shown in formulas **1**, **3**, and **4**. Evidently the carcinogenic metabolism of fluorine-containing DMBA derivatives is complicated.

The syntheses of 9- and 10-CF_3-DMBA's are described in Scheme I. Although, in general, the introduction of CF_3 groups has been accomplished by two methods,[6] little information[7] was available, at the outset of this work, on the stability of aromatic CF_3 groups toward reagents and conditions that were employed in the syntheses of **12** and **13**. Our work demonstrates that the Ar CF_3 group is less powerful than the oxazoline moiety in ortho-lithiation[7] reactions, is resistant to reducing agents such as $SnCl_2$–HCl, HI–H_3PO_2, Et_3SiH–CF_3CO_2H, and Zn–KOH, and is stable to $K_2Cr_2O_7$ in HOAc.

An alternate route to **12** that was unsuccessful is shown in Scheme II. Interestingly cyclization of **19** to **20** occurred in an acidic reducing medium (see Experimental Section) and is believed to have followed the same pathway as the HI-P reductive cyclizations.[8] However, attempts to cyclize **17** in $ZnCl_2$–acetic anhydride or **18** with PPA failed. In the latter cases the electron-attracting effect of the CF_3 group undoubtedly was responsible for the failures. Cyclization of **8** and **9** to give **10** and **11** (after oxidation) succeeded as ring closure involved a position in a naphthalene nucleus.

Experimental Section[9]

4,4-Dimethyl-2-(4-(trifluoromethyl)phenyl)-2-oxazoline (5).[9] The title compound, **5**, mp 36–37 °C, was prepared in 83% yield from *p*-(trifluoromethyl)benzoyl chloride (Sigma) as described.[10] M^+ = 243.087834; $C_{12}H_{12}F_3NO$ requires 243.087090.

3-(2-Naphthyl)-5-(trifluoromethyl)phthalide (6).[9] To a solution of **5** (5.0 g, 20.56 mmol) in 75 mL of dry ether, maintained at 0 °C under N_2, was added 15 mL of 1.4 M *n*-BuLi (Aldrich) in *n*-hexane. After stirring for 3.5 h at 0 °C, a solution of 3.35 g (21.45 mmol) of 2-naphthaldehyde (Aldrich, redistilled) in 20 mL of ether was introduced in one portion. The mixture was stirred at ambient temperature for 24 h and worked up as described[11] to obtain 6.85 g of crude adduct, mp 141–146 °C. This was hydrolyzed by refluxing with 20 mL of concentrated H_2SO_4, 14 mL of water, and 140 mL of ethanol for 3 h to yield, after crystallization from *n*-heptane, 3.5 g (52%) of **6**, mp 153–154 °C M^+ = 328.071816; $C_{19}H_{11}F_3O_2$ requires 328.071105.

3-(1-Naphthyl)-5-(trifluoromethyl)phthalide (7).[9] Use of freshly distilled 1-naphthaldehyde (Aldrich) instead of 2-naphthaldehyde in the above procedure afforded **7**, mp 111–112 °C (ethanol), in 53% yield. M^+ = 328.071816; $C_{19}H_{11}F_3O_2$ requires 328.071105.

2-(2-Napthylmethyl)-4-(trifluoromethyl)benzoic Acid (8).[9] To a well-stirred solution, at 0–10 °C, of 53 g (22.79 mmol) of 55% aqueous HI and 26.5 g (20.07 mmol) of 50% aqueous H_3PO_2 was added 161.6 g (1.58 mmol) of Ac_2O during 15 min. The phthalide **6** (3.0 g, 9.14 mmol) was then introduced and the contents held at reflux for 1.5 h, cooled, and poured onto ice to obtain, after crystallization from *n*-heptane, 2.8 g (93%) of **8**, mp 129–130 °C. M^+ = 330.087622; $C_{19}H_{13}F_3O_2$ requires 330.086755.

2-(1-Naphthylmethyl)-4-(trifluoromethyl)benzoic Acid (9).[9] Similarly **9**, mp 188–189 °C (*n*-heptane–benzene), was obtained in 98% yield from 3.2 g (9.7 mmol) of **7**. M^+ = 330.087622; $C_{19}H_{13}F_3O_2$ requires 330.086755.

9-(Trifluoromethyl)-7,12-benz[*a*]anthraquinone (10).[9] To 0.43 g (1.302 mmol) of **8** were added 6 mL of glacial HOAc, 3.5 mL of Ac_2O, and 0.1 g of $ZnCl_2$. The mixture was held at reflux for 2 h, after which 2 mL of water followed by 0.5 g of $K_2Cr_2O_7$ were carefully introduced. After refluxing further for 1 h, the cooled mixture was poured onto about 150 g of ice containing 4 mL of concentrated H_2SO_4 to give, after crystallization from benzene, 0.386 g (91%) of **10**, mp 223–224 °C. M^+ = 326.056275; $C_{19}H_9F_3O_2$ requires 326.055456.

10-(Trifluoromethyl)-7,12-benz[*a*]anthraquinone (11).[9] By following the above procedure, **11**, mp 199–200 °C (*n*-heptane–benzene), was obtained in 99% yield from 2.7 g (8.2 mmol) of **9**. M^+ = 326.056275; $C_{19}H_9F_3O_2$ requires 326.055456.

(6) Marhold, A.; Klauke, E. *J. Fluorine Chem.* **1981**, *18*, 281.
(7) Hudlický, M., "Organic Fluorine Chemistry"; Plenum Press: New York, 1971, pp 100, 110.
(8) (a) Platt, K. L.; Oesch, F. *J. Org. Chem.* **1982**, *47*, 5321. (b) *Ibid.*, **1981**, *46*, 2601.
(9) All new compounds had IR and/or ^1H NMR spectra consistent with the postulated structures. Microanalyses were performed by Galbraith Microanalytical Laboratories. The term "worked up as usual" means that an ether–benzene solution of the product was washed with dilute acid and/or alkali and then with saturated brine and filtered through anhydrous $MgSO_4$. The solvent was then removed on a rotary evaporator. All melting points are uncorrected.
(10) Meyers, A. I.; Temple, D. C.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.
(11) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008. Newman, M. S.; Kumar, S. *Ibid.* **1978**, *43*, 370.

7,12-Dihydro-7,12-dihydroxy-7,12-dimethyl-9-(trifluoromethyl)benz[*a*]anthracene (10a) and 7,12-Dimethyl-9-(trifluoromethyl)benz[*a*]anthracene (12).[9] To a solution of 2.0 g (6.1 mmol) of **10** in 30 mL of ether and 80 mL of benzene under N_2 was added 14.5 mL of 1.6 M MeLi (Aldrich) in ether.[12] The contents were held at reflux for 2.75 h and cooled, 20 mL of 10% NH_4Cl was introduced, and the mixture was worked up[9] as usual to obtain 1.8 g (82%) of **10a**, mp 170–176 °C (presumably a mixture of isomers). M^+ = 358.116980; $C_{21}H_{17}F_3O_2$ requires 358.118053.

Compound **10a** (1.8 g) was added, in five portions, to a well-stirred solution of 9.0 g of $SnCl_2$ and 5.4 mL of concentrated HCl in 100 mL of ether.[13] After stirring for 20 min, 50 mL of water was introduced. The usual workup gave, after chromatography over basic alumina and crystallization from EtOH–CH_2Cl_2, 1.05 g (64%) of **12**, mp 172–173 °C. M^+ = 324.113330; $C_{21}H_{15}F_3$ requires 324.112576. Anal. Calcd for $C_{21}H_{15}F_3$: C, 77.8; H, 4.7. Found: C, 77.8; H, 4.7.

7,12-Dihydro-7,12-dihydroxy-7,12-dimethyl-10-(trifluoromethyl)benz[*a*]anthracene (11a) and 7,12-Dimethyl-10-(trifluoromethyl)benz[*a*]anthracene (13).[9] Following the above procedure, 2.5 g (7.7 mmol) of **11** gave 2.45 g of crude **11a** which on reduction with $SnCl_2$–HCl afforded, after chromatography over basic alumina and crystallization from EtOH–CH_2Cl_2, 1.28 g (51% from **11**) of **13**, mp 102.5–103.5 °C. M^+ = 324.113330; $C_{21}H_{15}F_3$ requires 324.112576. Anal. Calcd for $C_{21}H_{15}F_3$: C, 77.8; H, 4.7. Found: C, 77.5; H, 4.9.

2-(3-(Trifluoromethyl)benzoyl)-1-naphthoic Acid (15).[9] To Mg (sublimed, 1.25 g, 0.054 mol) in 10 mL of dry ether was added 1,2-dibromoethane (1.0 g, 0.0053 mol) in 5 mL of ether. After the exothermic reaction had started, *m*-(trifluoromethyl)bromobenzene[14] (10.0 g, 0.0444 mol) in 75 mL of ether was added over 1 h. The contents were refluxed for 1 h, cooled, and forced[15] under N_2 into an addition funnel.

To a refluxing solution of 1,2-naphthalic anhydride[16] (8.8 g, 0.0444 mol) and TMEDA (5.16 g, 0.0444 mol) in 140 mL of dry benzene was added, during 1 h, the above Grignard reagent.[17] The contents were held at reflux for 18 h, cooled, acidified, and separated into acid and neutral fractions using aqueous diethanolamine. From the acid fraction there was obtained 5.8 g (38%) of **15**, mp 148–150 °C (*n*-heptane–CH_2Cl_2). M^+ = 344; $C_{19}H_{11}F_3O_3$ requires 344. Anal. Calcd for $C_{19}H_{11}F_3O_3$: C, 66.3; H, 3.2; F, 16.6. Found: C, 66.2; H, 3.5; F, 16.4.

2-[1-Hydroxy-1-(3-(trifluoromethyl)phenyl)ethyl]-1-naphthoic Acid Lactone (16).[9] To a solution of 2.53 g (7.35 mmol) of **15** in 125 mL of dry benzene was added, during 5 min, 7.5 mL of MeMgBr (Aldrich, 2.5 M in ether).[17] The contents were stirred at ambient temperature for 2 h, refluxed for 30 min, cooled, and worked up to obtain 1.85 g (74%) of **16**, mp 99–101 °C (*n*-hexane). M^+ = 342.087156, $C_{20}H_{13}F_3O_2$ requires 342.086755.

2-[1-(3-(Trifluoromethyl)phenyl)ethyl]-1-naphthoic Acid (17).[9] A well-stirred mixture of 1.0 g (2.92 mmol) of **16** in 10 mL of pyridine, 10 mL of 20% KOH, 50 mg of $CuSO_4 \cdot 5H_2O$, and 15 g of activated[18] zinc was held at reflux for 7 h and filtered hot through Celite and the filtrate was cooled, acidified, and separated into neutral and acid fractions to obtain 0.38 g of **16** and 0.56 g (89%, based on unrecovered **16**) of **17**, mp 123–124 °C (*n*-heptane). M^+ = 344.103225; $C_{20}H_{15}F_3O_2$ requires 344.102404.

1-Acetyl-2-[1-(3-(trifluoromethyl)phenyl)ethyl]-naphthalene (18).[9] To 1.71 g (5.0 mmol) of **17** in 30 mL of benzene was added 1.2 g (10.0 mmol) of $SOCl_2$ and the contents refluxed for 3.5 h. The solvent and excess $SOCl_2$ were then removed in vacuo to obtain the acid chloride, which was dissolved in 10 mL of ether and added to a solution of Me_2CuLi[19] (prepared from 2.85 g (15 mmol) of CuI in 50 mL of ether and 20 mL of 1.5 M ethereal MeLi (30 mmol)) at −78 °C under argon. The solution was stirred for 35 min at −78 °C and then quenched with 5 mL each of methanol and saturated NH_4Cl solution. The usual workup and chromatography over neutral alumina afforded 1.25 g (74%) of **18**, mp 100–101.5 °C (*n*-hexane). M^+ = 342.123850; $C_{21}H_{17}F_3O$ requires 342.123139.

Attempted Cyclization of 18. PPA cyclization at 70 °C and 120 °C led to the recovery of starting ketone in 70% and 36% yields, respectively. The compound (0.1 g) decomposed when refluxed for 1.5 h with 0.1 g of $ZnCl_2$ and 5 mL of propionic anhydride.

2-[(3-(Trifluoromethyl)phenyl)hydroxymethyl]-1-naphthoic Acid Lactone (19).[9] A solution of 2.3 g (6.7 mmol) of **15** in 40 mL of CF_3CO_2H (99%, Aldrich) was treated with 4.0 g (34.4 mmol) of Et_3SiH[20] and stirred at ambient temperature for 48 h after which the CF_3CO_2H was removed in vacuo and the residue chromatographed on silica gel to obtain 1.9 g (87%) of **19**, mp 130–131 °C (*n*-heptane). M^+ = 328.072080; $C_{19}H_{11}F_3O_2$ requires 328.071105.

9-(Trifluoromethyl)benz[*a*]anthracene (20).[9] A mixture of 1.19 g (3.6 mmol) of **19**, 15 g of 55% HI, 15 g of 50% H_3PO_2, and 83 g of Ac_2O[21] was refluxed for 72 h, after which most of the solvent was distilled off, the contents poured onto ice, and the solid filtered and separated into acid (0.28 g) and neutral (0.8 g) fractions.[22] Chromatography of the neutral fraction on silica gel afforded 0.35 g (33%) of **20**, mp 180–182 °C. M^+ = 296.082388; $C_{19}H_{11}F_3$ requires 296.081277. Confirmation of this structure was secured by oxidation to **10** in 61% yield using $K_2Cr_2O_7$ as described earlier.

Registry No. **5**, 86727-72-2; **5** 2-naphthaldehyde adduct, 86727-73-3; **6**, 86727-74-4; **7**, 86727-75-5; **8**, 86727-76-6; **9**, 86727-77-7; **10**, 86727-78-8; **10a**, 86727-79-9; **11**, 86727-80-2; **11a**, 86727-81-3; **12**, 86727-82-4; **13**, 86727-83-5; **15**, 86727-84-6; **16**, 86727-85-7; **17**, 86727-86-8; **17** acid chloride, 86727-87-9; **18**, 86727-88-0; **19**, 86727-89-1; **20**, 86727-90-4; 2-naphthaldehyde, 66-99-9; 1-naphthaldehyde, 66-77-3; *m*-(trifluoromethyl)bromobenzene, 401-78-5; 1,2-naphthalic anhydride, 5343-99-7.

(12) Compare: Newman, M. S.; Khanna, J. M.; Kanakarajan, K.; Kumar, S. *J. Org. Chem.* **1978**, *43*, 2553.

(13) Newman, M. S.; Kanakarajan, K. *J. Org. Chem.* **1980**, *45*, 2301.

(14) We thank Rhône-Poulenc Industries for a generous gift of *m*-(trifluoromethyl)bromobenzene. For Grignard reactions of *m*-(trifluoromethyl)bromobenzene see: Gilman, H.; Tolman, L.; Yeoman, F.; Woods, L. A.; Shirley, D. A.; Avakian, S. *J. Am. Chem. Soc.* **1946**, *68*, 426. Simons, J. H.; Ramler, E. O. *Ibid.* **1943**, *65*, 389.

(15) This technique is described in: Newman, M. S. "An Advanced Organic Laboratory Course"; Macmillan: New York, 1972, pp 113–114.

(16) For a convenient synthesis of 1,2-naphthalic anhydride see: Newman, M. S.; Dhawan, B.; Hashem, M. M.; Khanna, V. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 3925.

(17) Compare: Newman, M. S.; Swaminathan, S.; Chatterji, R. *J. Org. Chem.* **1959**, *24*, 1961.

(18) Commercial zinc was activated by successive treatment with 12% HCl (for ca. 20 min), H_2O, 25% $CuSO_4$, and H_2O.

(19) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**, 4647.

(20) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

(21) Just enough to react with the water present in HI and H_3PO_2 to give HOAc so that the reaction is carried out essentially under water-free conditions.

(22) Compare: Harvey, R. G.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.* **1982**, *47*, 2120.