stirrer, a condenser and a dropping funnel, and containing 9.5 g. (0.1 mole) of 2-aminopyrimidine[1] in 30 ml. of dry pyridine, 19.4 g. (0.1 mole) of *p*-fluorobenzenesulfonyl chloride was added with stirring. The mixture was heated at 120° for 2 hours and a solution of 4.4 g. (0.11 mole) of sodium hydroxide in 25 ml. of water was then added slowly with continued heating. The pyridine was removed by distillation under reduced pressure, water being added from time to time to maintain the volume approximately constant. The product which separated was filtered, washed well with water, and air-dried. The yield of pure 2-(*p*-fluorobenzenesulfonamido)-pyrimidine, m.p. 184.5–185.0°, was 14.6 g. (57.7%).

Anal. Calcd. for $C_{10}H_8O_2N_3SF$: N, 16.6. Found: N, 16.5.

2-(*p*-Fluorobenzenesulfonamido)-thiazole.—This compound was prepared by the method used for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine except that 10.0 g. (0.1 mole) of 2-aminothiazole was substituted for the 2-aminopyrimidine. The crude material was recrystallized from glacial acetic acid to yield 15.5 g. (60.1%) of product melting at 171.2–172.0°,

Anal. Calcd. for $C_9H_7O_2N_2SF$: N, 10.9. Found: N, 10.7.

2-(*p*-Fluorobenzenesulfonamido)-pyridine.—This product was prepared by the method described for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine, except that 9.4 g. (0.1 mole) of 2-aminopyridine was used in place of 2-aminopyrimidine. The crude product (23 g.) was recrystallized repeatedly from glacial acetic acid to give 5.3 g. (21.0%) of pure material, melting at 151.2–151.7°.

Anal. Calcd. for $C_{11}H_9O_2N_2SF$: N, 11.1. Found: N, 11.0.

p-Fluorobenzoic Acid.—This product, m.p. 184.1–184.7°,[2] was prepared in 70% yield from *p*-fluorotoluene[3] according to the directions given by Clark and Taylor[4] for the oxidation of *o*-chlorotoluene to *o*-chlorobenzoic acid.

2-(*p*-Fluorobenzamido)-pyridine.—This compound was prepared from 2-aminopyridine and *p*-fluorobenzoyl chloride[5] by the general method described for 2-(*p*-fluorobenzenesulfonamido)-pyrimidine. The crude material was recrystallized from alcohol–water. The yield of pure product, m.p. 123.6–124.3°, was 62%.

Anal. Calcd. for $C_{12}H_9ON_2F$: N, 12.9. Found: N, 12.7.

2-(*p*-Fluorobenzamido)-thiazole.—Prepared by the usual method, this compound, m.p. 186.2–186.8° after recrystallization from alcohol–water, was obtained in 75% yield.

Anal. Calcd. for $C_{10}H_7ON_2FS$: N, 12.6. Found: N, 12.5.

2-(*p*-Fluorobenzamido)-pyrimidine.—To a mixture of 2.7 g. (0.028 mole) of 2-aminopyrimidine, 5.4 g. (0.028 mole) of powdered potassium carbonate, and 50 ml. of dry ether contained in a 200-ml. conically shaped 3-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, 4.4 g. of *p*-fluorobenzoyl chloride was added dropwise with stirring. The mixture was heated under reflux on a steam-bath for 3 hours. The solid remaining after removal of the ether and addition of 50 ml. of water was filtered and air dried to give 5.6 g. (91%) of crude material. This was dissolved in benzene, extracted with 5% hydrochloric acid and the benzene solution dried over anhydrous sodium sulfate. Addition of Skellysolve C to the benzene solution gave 4.8 g. (80.0%) of a colorless product, m.p. 224.4–226.0°.

Anal. Calcd. for $C_{11}H_8ON_3F$: C, 60.8; H, 3.7. Found: C, 60.6; H, 3.7.

(1) Obtained through the kindness of the Calco Chemical Division of the American Cyanamid Co.

(2) G. Schiemann and W. Winkelmüller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 299, reported 186°.

(3) B.p. 114–115° at 728 mm. Prepared in 71% yield by diazotization of *p*-toluidine in anhydrous hydrogen fluoride, followed by decomposition of the resulting diazonium fluoride in refluxing hydrogen fluoride.

(4) H. T. Clarke and E. R. Taylor, ref. 2, p. 135.

(5) Prepared by reaction of *p*-fluorobenzoic acid with thionyl chloride.

Discussion.—The compounds were tested *in vitro* as antagonists of the growth of *Staphylococcus aureus*, using Klinger medium and of *Escherichia coli*, using MacLeod medium. The organisms were inoculated, at the peak of their growth curves, into Klett–Summerson tubes containing standard drug concentrations. The tubes were incubated at 37° for 24 hours, and growth was determined by means of a Klett–Summerson photoelectric colorimeter. The minimal effective concentrations necessary to inhibit completely the growth of the organism are shown in Table I. Data for sulfathiazole and sulfasuxadine are added for comparison purposes.

TABLE I

Compound	Minimal effective concentration, *M* *E. coli*	*S. aureus*
p-Fluorobenzenesulfonamide	1×10^{-2}	
2-(*p*-Fluorobenzenesulfonamido)-pyridine	1×10^{-3}	
2-(*p*-Fluorobenzenesulfonamido)-pyrimidine	1×10^{-3}	
2-(*p*-Fluorobenzenesulfonamido)-thiazole	1×10^{-3}	1×10^{-4}
p-Fluorobenzoic acid	1×10^{-2}	1×10^{-2}
p-Fluorobenzamide[a]	1×10^{-1}	1×10^{-2}
Sulfathiazole	1×10^{-4}	4×10^{-6}
Sulfasuxadine	2×10^{-2}	

[a] Prepared by the method of J. H. Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

It is noteworthy that the inhibition of growth on *Escherichia coli* produced by *p*-fluorobenzoic acid was not reversed by its isostere *p*-aminobenzoic acid, but was reversed by tyrosine. The *p*-fluorobenzamides of 2-aminopyridine, 2-aminopyrimidine and 2-aminothiazole were not sufficiently soluble in the media to be tested.

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The Mechanism of Addition of Grignard Reagents to Ketones

BY C. GARDNER SWAIN AND HENRY B. BOYLES

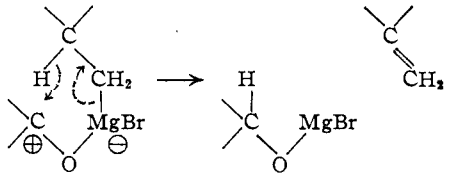
By testing a prediction from a mechanism based on kinetic studies of a model system which did not involve diisopropyl ketone at all, we have succeeded in increasing the yield of addition product in the reaction of *n*-propylmagnesium bromide with diisopropyl ketone from 36[1] to 65%.

This prediction was based on a consideration of the difference between the most probable mechanism for *addition of Grignard reagents to ketones* and the most probable mechanism for *reduction*, which is the principal competing side reaction. From other simple mechanisms which might be assumed to hold for these two processes, one would have predicted either no effect or a lower yield of addition by the new procedure; hence, the

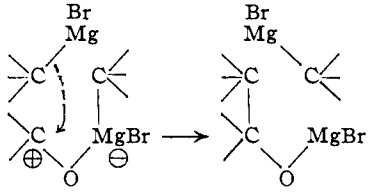
(1) Whitmore and George, THIS JOURNAL, **64**, 1239 (1942).

success of the prediction is evidence for the correctness of the mechanisms originally assumed. These are outlined briefly below.

The mechanism for *reduction* involves an internal *cyclic* rearrangement of a complex.[2]



However, the mechanism for *addition of Grignard reagents to ketones* must be different for reasons previously given[3] and appears to involve reaction of the Grignard-ketone complex with a *second* molecule of Grignard reagent.



This mechanism unambiguously predicts that one should be able to increase the yield of addition to a hindered ketone at the expense of reduction by the simple expedient of adding magnesium bromide to the ketone prior to addition of the Grignard reagent. Magnesium bromide is a slightly stronger Lewis acid than the Grignard reagent and should complex preferentially with the ketone, polarizing it even more strongly than would a Grignard reagent. Thus it would tend to play the role of the first molecule of Grignard reagent (which complexes with the ketone) in the normal Grignard-ketone addition mechanism. The magnesium bromide–ketone complex would be incapable of reduction by intramolecular rearrangement, but possibly even more susceptible than a Grignard-ketone complex to attack by an external molecule of Grignard reagent.

To test this prediction we selected the reaction of *n*-propylmagnesium bromide with diisopropyl ketone, which was reported by Whitmore and George to give 36% addition, 60% reduction and 2% enolization when carried out in the normal way.

n-Propylmagnesium bromide was added to diisopropyl ketone (1) with nothing else added, to check the results of Whitmore and George,[1] (2) after mixing an ether solution of more than equivalent magnesium bromide with the ketone to complex with it, and (3) after adding only ether, to show that the effect produced in (2) was not one of dilution. The reaction conditions were identical and the products were hydrolyzed in the same manner in each case. The yields found were (1) 30% addition, 63% reduction, 3% enolization; (2) 65% addition, 26% reduction, 1% enolization; (3) 29% addition, 66% reduction, 2% enolization. Evidently the addition of magnesium bromide in (2) favors the addition reaction at the expense of the reduction reaction.

The success of this prediction is additional evidence for the correctness of the mechanism on which it was based.

We plan to test the synthetic utility of this technique in even more hindered cases, such as the Grignard synthesis of triisopropyl- and tri-*t*-butylcarbinols. It may prove advantageous to substitute magnesium iodide or other Lewis acids for the magnesium bromide.

(2) The mechanism pictured is consistent with the findings of Kharasch and Weinhouse (*J. Org. Chem.*, **1**, 209 (1936)). Although solvation of magnesium is not shown here, it is understood that the magnesium atom of the reactant is coördinated with an ether molecule, and that the attack of a second ether molecule may contribute to the rupture of the Mg–C bond.

(3) Swain, THIS JOURNAL, **69**, 2306, 2308 (1947); *cf.* also Swain and Kent, *ibid.*, **72**, 518 (1950).

Experimental

Reagents.—*n*-Propylmagnesium bromide was made by adding 185 g. (1.50 moles) of freshly distilled *n*-propyl bromide slowly to 38 g. (1.56 moles) of magnesium turnings in 450 cc. of dry ether. After settling overnight the supernatant liquid was siphoned into 200-cc. narrow-mouth screw-cap bottles under a nitrogen atmosphere. The bottles were stored at 5°.

Diisopropyl ketone was redistilled through a four-foot column packed with glass helices at a reflux ratio of 20:1, b.p. 122.9–123.2°, n^{20}D 1.4001, n^{25}D 1.3980 (reported[1,4] b.p. 123.7°, n^{20}D 1.4002).

Diisopropylcarbinol was redistilled through the same column, b.p. 139–140°, n^{20}D 1.4229, n^{25}D 1.4209 (reported[4] b.p. 140°, n^{20}D 1.4226).

Analysis of Mixtures of Diisopropylcarbinol and Diisopropyl Ketone.—The per cent. carbinol in the distilled *s*-carbinol–ketone fraction of the reaction products was determined by refractive index, by comparison with a plot of composition *vs.* refractive index prepared from standard mixtures of the pure components.

Reaction with Ketone, Magnesium Bromide and Grignard Reagent.—Bromine (113 g., 0.71 mole) was added slowly with continuous stirring to 17.2 g. (0.71 mole) of magnesium and 210 cc. of ether using a sealed nichrome wire stirrer and a slight positive static pressure of dry nitrogen. Finally, the bromine color disappeared. The magnesium bromide was not all in solution, since its solubility in ether is less than 0.2 *M*.[5] Diisopropyl ketone (35.9 g., 0.314 mole) was added over a period of 1 hour with stirring, and stirred 1 hour more. Then *n*-propylmagnesium bromide (0.6 mole in 210 cc. of ether) was added to the mixture over 1 hour, and stirred 1 hour more. The mixture was hydrolyzed by adding it slowly to 830 cc. of 10% sodium carbonate solution at 0° with good stirring. The ether was distilled from the ether layer and 600 cc. of ether extracts in a Claisen flask, and the residue (43.9 g.) was distilled at 115 mm. through an 18-inch column packed with small stainless steel helices at a reflux ratio of 15:1. The fractions obtained were 10.1 g. of a mixture of diisopropyl ketone and diisopropylcarbinol, b.p. 80–90° at 115 mm., and 32.5 g. (0.205 mole) of *n*-propyldiisopropylcarbinol, b.p. 121–122° at 115 mm. The separation was very sharp, with less than 1 cc. distilling between 95 and 115°. The mixture had a refractive index n^{20}D 1.4200, hence contained 9.7 g. (0.083 mole, 26%) of diisopropylcarbinol and 0.4 g. (0.003 mole, 1%) of diisopropyl ketone. The *n*-propyldiisopropylcarbinol (65% yield) was identified by boiling point, refractive index n^{25}D 1.4401 and analysis.

Anal. Calcd. for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.62; H, 13.92.

Reactions without Magnesium Bromide.—*n*-Propylmagnesium bromide (0.6 mole in 210 cc. ether) was added in the same way to either pure diisopropyl ketone or 33.4 g. (0.292 mole) of the ketone mixed with 210 cc. of ether. The products were worked up as before. In the latter case they totaled 37.0 g., and were separated into 23.0 g. of a mixture of diisopropylcarbinol and diisopropyl ketone, b.p. 78–85° at 110 mm., and 13.5 g. (0.0874 mole) of *n*-propyldiisopropylcarbinol, b.p. 104° at 60 mm. The mixture had

(4) Poletaeff, *Ber.*, **24**, 1309 (1891).

(5) Menshutkin, *Z. anorg. Chem.*, **49**, 34 (1906).

$n^{25}D$ 1.4202, hence contained 22.4 g. (0.193 mole, 66%) of diisopropylcarbinol and 0.6 g. (0.005 mole, 2%) of diisopropyl ketone. The *n*-propyldiisopropylcarbinol (29%) was identified by b.p. and refractive index $n^{25}D$ 1.4400.

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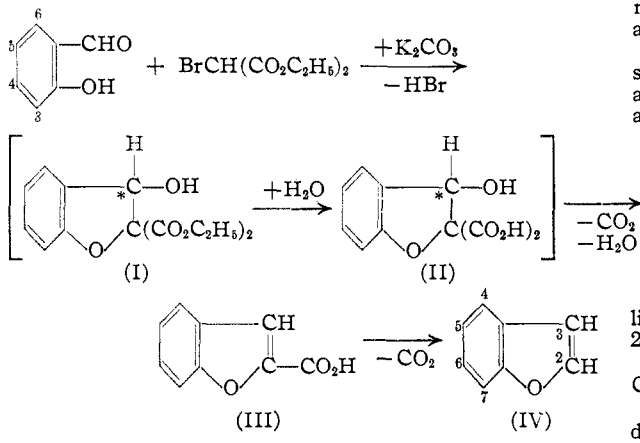
Coumarones from *o*-Hydroxyaldehydes and Bromomalonic Ester

BY SANAE TANAKA

This paper describes the results obtained in substituting ethyl bromomalonate for ethyl bromoacetate in the coumarone synthesis from *o*-hydroxyaldehydes.[1,4] The reaction is given in the scheme



Salicylaldehyde and ethyl bromomalonate refluxed in methyl ethyl ketone[2] in the presence of potassium carbonate condense to give DL-3-hydroxycoumaran-2,2-dicarboxylic acid ester (I). This product was converted without isolation to DL-3-hydroxycoumarandicarboxylic acid (II), which in turn was converted to coumarilic acid (III) on decarboxylation and dehydration. The salicylaldehyde has been replaced with its 4-methoxy, 5-methoxy and 4,5-dimethoxy derivatives. The yields of crude coumarilic acid and its derivatives range from 72–90%. The coumarilic acids have been decarboxylated in quinoline with copper powder[3] and gave coumarone (IV) and the corresponding derivatives, isolated in some cases as their picrates, in 80–93% yields. With *o*-hydroxyacetophenone a 38% yield of 3-methylcoumarilic acid was obtained. It has been shown previously[4] that isolation of the intermediate products I and II decreases over-all yields.

Experimental

Coumarilic Acid (III).—Salicylaldehyde (2.5 g.), ethyl bromomalonate[5] (5 g.), anhydrous potassium carbonate (2.5 g.) and methyl ethyl ketone (10 ml.) were mixed together and the whole was refluxed for 5 hours on a steam-bath. After distilling off the main part of the solvent, the residue was mixed with water and acidified with dilute sulfuric acid and then extracted with ether. The ethereal extract, after removal of the solvent, was dissolved in alcoholic potash (alcohol 20 ml., potassium hydroxide 2 g.) and then refluxed on a steam-bath for 1 hour. After concentrating to a small volume the residue was dissolved in water and acidified with dilute sulfuric acid. The colorless crystals thus formed were collected, washed with water and dried. Recrystallization from benzene gave colorless long plates; yield 2.5 g. (76%); m.p. 192–193°.[6]

Anal. Calcd. for $C_9H_8O_3$: C, 66.66; H, 3.70. Found: C, 66.45; H, 3.67.

Coumarone (IV).—Coumarilic acid (0.5 g.) and copper powder (0.1 g.) were refluxed in quinoline (10 ml.) for 30 minutes. After cooling ether was added, the mixture filtered from copper, then washed several times with 2 *N* hydrochloric acid, then with water to remove quinoline. This ethereal extract, when freed from the solvent, gave coumarone as an oil which possesses a guaiacol-like odor. It was warmed with picric acid. The coumarone picrate thus obtained was recrystallized from dilute alcohol; yield 0.75 g. (80%) yellow columns; m.p. 102–103°.[7] No melting point depression was observed when mixed with an authentic specimen.

6-Methoxycoumarilic Acid.—4-Methoxysalicylaldehyde[4b] substituted for salicylaldehyde gives 6-methoxycoumarilic acid in 90% yield, m.p. 206°,[8] recrystallized from ethyl acetate.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.48; H, 4.19. Found: C, 62.31; H, 3.98.

6-Methoxycoumarone.—6-Methoxycoumarilic acid was decarboxylated by the technique described above. The product was isolated in its picrate, m.p. 64°.[9]

Anal. Calcd. for $C_9H_8O_2 \cdot C_6H_3O_7N_3$: N, 11.14. Found: N, 10.93.

5-Methoxycoumarilic Acid.—5-Methoxysalicylaldehyde[10] likewise gives 5-methoxycoumarilic acid in 72% yield, m.p. 212–213°, recrystallized from acetone.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.48; H, 4.19. Found: C, 62.61; H, 4.29.

5-Methoxycoumarone.—5-Methoxycoumarilic acid upon decarboxylation gave 5-methoxycoumarone in 93% yield, m.p. 32–33°, b.p. 120–125° (30 mm.).

Anal. Calcd. for $C_9H_8O_2$: C, 72.97; H, 5.45. Found: C, 73.25; H, 5.49.

5,6-Dimethoxycoumarilic Acid.—4,5-Dimethoxysalicylaldehyde[11] similarly gave 5,6-dimethoxycoumarilic acid, in 80% yield, m.p. 245° (dec.), recrystallized from alcohol.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.48; H, 4.65.

5,6-Dimethoxycoumarone.—5,6-Dimethoxycoumarilic acid through decarboxylation gave 5,6-dimethoxycoumarone in 90% yield, m.p. 53–54°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.62. Found: C, 67.31; H, 5.66.

3-Methylcoumarilic Acid.—*o*-Hydroxyacetophenone, when condensed with ethyl bromomalonate, afforded 3-methylcoumarilic acid in 38% yield, the melting point of which (188.5–189.5° from diluted alcohol) coincides with those given by Hantzsch[12] or Peter.[13]

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.54. Found: C, 68.36; H, 4.68.

Further attempts to attain 3-methylcoumarone were abandoned owing to the scarcity of the material.

Acknowledgment.—The author wishes to express his gratitude to Prof. Sin'iti Kawai, under whose suggestion this work was undertaken. He is also indebted to the research fund awarded for him from the Department of Education.

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(1) Kostanecki, *Ber.*, **42**, 901 (1909); **43**, 2155 (1910).

(2) Acetone can be used instead but somewhat poorer yields of coumarilic acid result.

(3) Shepard, THIS JOURNAL, **52**, 2083 (1930).

(4) (a) Kawai, Nakamura and Sugiyama, *Ber.*, **72**, 1146 (1939); (b) Kawai, Nakamura and Yoshida, *ibid.*, **73**, 581 (1940).

(5) "Organic Syntheses," Vol. VII, p. 34 (1927).

(6) Perkin [*J. Chem. Soc.*, **24**, 45 (1871)] gave m. p. 192–193°.

(7) Kraemer [*Ber.*, **23**, 3276 (1890)] described m.p. 102–103°.

(8) Robertson [*J. Chem. Soc.*, 787 (1940)] described m.p. 206°.

(9) Anderson [THIS JOURNAL, **60**, 1419 (1938)] described m.p. 64–65°.

(10) Rubenstein, *J. Chem. Soc.*, **127**, 1999 (1925).

(11) Robertson, *ibid.*, 2434 (1930).

(12) Hantzsch, *Ber.*, **19**, 1292 (1886); m.p. 188–189°.

(13) Peter, *ibid.*, **41**, 832 (1908); m.p. 188°.