

Evans Chemistry Laboratory, Ohio State University

A New Synthesis of 3-Chloroflavones(1)

Melvin S. Newman, John L. Ferrari(2) and C. P. Garg(2)

The synthesis of a number of 3-chloroflavones by a new method, involving reaction of arylmagnesium bromides with 3,4-dichlorocoumarins, is described. The synthesis of 2-chloro-7-methyl-11H-benzofuro[3,2-b] [1]benzopyran-11-one is also described.

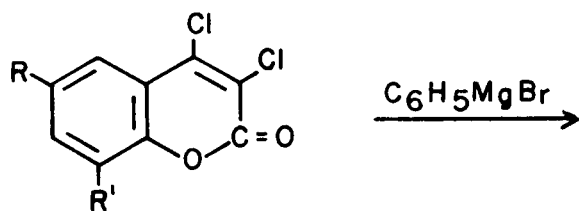
In a previous communication, the reaction of some 3,4-dichlorocoumarins with phenylmagnesium bromide to form 3-chloroflavones was announced (3). In this article these reactions are described in more detail as well as the use of such a condensation in a sequence of reactions to form a benzofurobenzopyranone.

The 3,4-dichlorocoumarins (I) were converted into the 3-chloroflavones (II) in good yields by treatment with phenylmagnesium bromide in benzene-ether solution. The yield was less when tetrahydrofuran was the solvent. The use of one equivalent of ethylene dibromide during the preparation of Grignard reagents (5) was harmful as smaller yields (or in some cases, no yield) resulted.

The fact that chloroflavones were produced rather

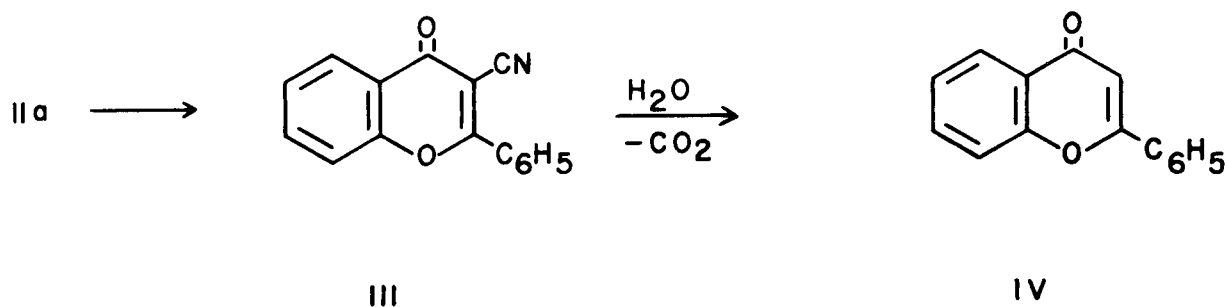
than the isomeric 3-chloro-4-phenylcoumarins was unexpected since all other nucleophilic reagents studied reacted to displace the 4-chlorine atom in compounds of type I (4,6) and yield 4-substituted coumarins.

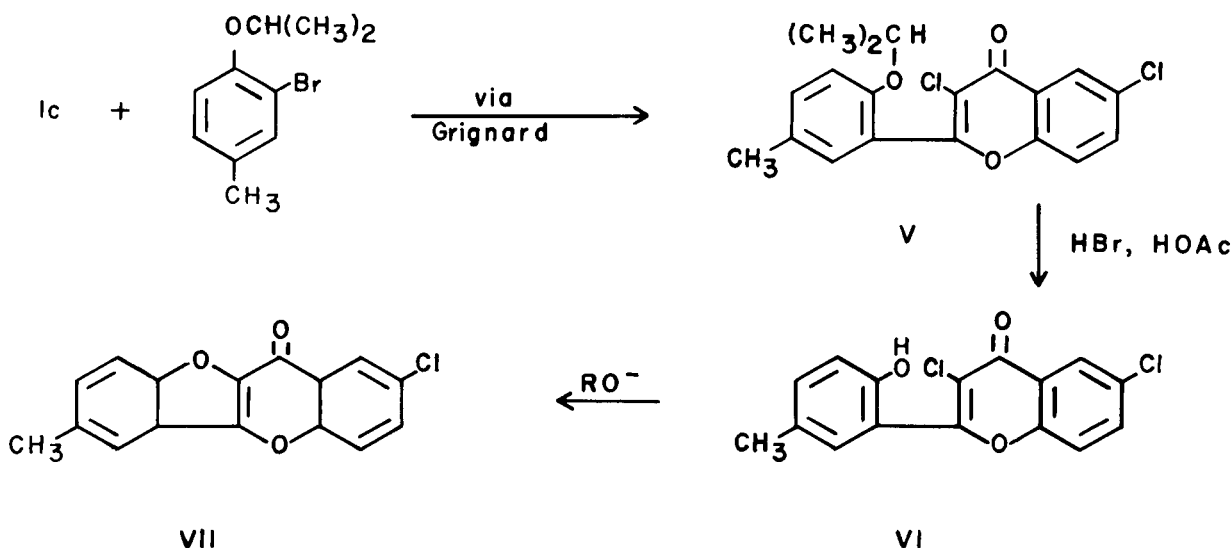
In order to establish the structure of compounds IIa,b,c as indicated, IIa was converted into the corresponding cyano compound, III, by heating with cuprous cyanide in N-methylpyrrolidone (7). On hydrolysis of III decarboxylation of the resulting acid occurred and the flavone, IV, identical with an authentic sample (8) (I.R. band at 6.16μ), was obtained. The carbonyl absorption for dichlorocoumarins (Ia,b,c) occurs at 5.76 , 5.89 , and 5.77μ , respectively, whereas in IIa,b,c it occurs at 6.07 , 6.03 and 6.07μ . The structures of the other flavones are assumed to be correct in



- I
- a ($R = R' = H$)
 - b ($R = CH_3, R' = H$)
 - c ($R = Cl, R' = H$)
 - d ($R = CH_3, R' = C_6H_5CO$)

- II
- a, b, c, d $Ar = C_6H_5$
 - e, $R = R' = H, Ar = 1-C_{10}H_7$
 - f, $R = Cl, R' = H$
 - $Ar = 2, 4, 6-(CH_3)_3C_6H_2$





EXPERIMENTAL (10)

view of this proof of structure for IIa.

When methylmagnesium bromide was used instead of phenylmagnesium bromide, mainly starting dichlorocoumarin, Ia, was recovered. No other aliphatic Grignard reagents were tried. When 4-chlorocoumarin and 4-chloro-3-methylcoumarin were used in place of Ia, no appreciable reaction with phenylmagnesium bromide took place and the starting materials were recovered in good yield. These results indicate that the nature of the group in the 3-position exerts a large influence on the reaction under discussion. Apparently, a chlorine in the 3-position is important for the success of the reaction leading to flavone formation.

In general Ia and Ic gave higher yields of the corresponding flavones, IIa,c, than did Ib. These facts coupled with the unreactivity of 4-chlorocoumarin indicate that electron withdrawing groups in the coumarin moiety favor the flavone synthesis herein described.

On treatment of Ia in aqueous acetic acid with zinc dust, a good yield of 3-chlorocoumarin was obtained. Thus, the reactivity of the 4-chlorine atom toward a reducing agent is shown, but no other reducing agents were tried.

Since 1-naphthylmagnesium bromide reacted with Ia and 2-isopropoxy-5-methylphenylmagnesium and mesitylmagnesium bromides reacted with Ic in good yields to give the expected flavones, IIe, f and V, respectively, the new chloroflavone synthesis appears general. This type of Grignard reaction was then used in the synthesis of 2-chloro-7-methyl-11H-benzofuro[3,2-b][1]benzopyran-11-one, VII as shown below.

The isopropyl group was chosen in place of the more conventional methyl group as protection for the phenolic function of 2-bromo-4-methylphenyl because of the greater ease of removal in step V → VI. Although minimal conditions for the cleavage were not worked out, refluxing for four hours in acetic acid containing a small amount of hydrobromic acid afforded VI in high yield. The cyclization of VI to VII was effected by heating in *t*-butyl alcohol containing potassium *t*-butoxide. To our knowledge, this represents the first synthesis of this ring system in this state of oxidation (9).

3-Chloroflavones (IIa,b,c).

In a typical experiment, the Grignard reagent from 8.8 g. of bromobenzene in 80 ml. of ether was added slowly to a stirred saturated solution of 10 g. of 3,4-dichlorocoumarin, Ia, in benzene at room temperature. The mixture became yellow and a yellow solid separated. After stirring for 10 hrs. the mixture was treated with dilute hydrochloric acid and worked up as usual. The solvents were concentrated under reduced pressure to a small volume and cyclohexane added. On continuation of the concentration a point was reached at which the solution became dark and a purple residue was observed. A few ml. of benzene were added and, on warming, spontaneous evolution of hydrogen chloride started. By the time the hydrogen chloride evolution was complete (a few minutes) the color was yellow. This solution was treated with Darco G-60 (activated charcoal) and filtered. A total of 9.1 g. (76%) of IIa, m.p. 121-123.5°, was obtained in two crops as colorless needles. The analytical sample, m.p. 121.8-123.2°, was obtained on recrystallization from benzene-cyclohexane.

Anal. Calcd. for C₁₅H₉ClO₂: C, 70.2; H, 3.5; Cl, 13.8. Found: C, 70.2; H, 3.4; Cl, 13.8.

By a similar procedure Ib was converted into 3-chloro-6-methylflavone, IIb, m.p. 132-136°, in 52% yield. The analytical sample, m.p. 135.0-136.6°, was obtained by recrystallization from ethanol.

Anal. Calcd. for C₁₆H₁₁ClO₂: C, 71.0; H, 4.1; Cl, 13.1. Found: C, 71.0; H, 3.8; Cl, 12.9.

Similarly Ic was converted into 3,6-dichloroflavone, IIc, m.p. 186-190°, in 72% yield suitable for further use. The analytical sample, m.p., 196.0-197.5° was obtained by vacuum sublimation at 160-170° at 3 mm.

Anal. Calcd. for C₁₅H₇Cl₂O₂: C, 61.9; H, 2.8; Cl, 24.4. Found: C, 62.0; H, 2.5; Cl, 24.2.

3,4-Dichloro-6-methyl-8-benzoylcoumarin (Id).

To a stirred solution of 60 g. of anhydrous aluminum chloride in 120 ml. of pure nitroethane was added 42.4 g. of 2-hydroxy-5-methylbenzophenone. After stirring at room temperature for 15 min., 50 g. of hexachloropropene was added dropwise. After addition was complete the mixture was stirred for 1.5 hr. and then heated to 70° for 2 hr. The reaction mixture was cooled and added to crushed ice (copious evolution of hydrogen chloride). After the usual work-up there was isolated 58.3 g. (92%) of Id, m.p. 164-167°, on crystallization from ethanol-benzene (charcoal). The analytical sample melted at 165.4-166.8° (I.R. bands at 5.85, 6.07 μ).

Anal. Calcd. for C₁₇H₁₀Cl₂O₃: C, 61.3; H, 3.0; Cl, 21.3. Found: C, 61.1; H, 3.0; Cl, 21.2.

When a similar condensation was attempted on *p*-hydroxybenzophenone a red-brown oil was obtained from which, after recrystallization from cyclohexane, was obtained 14.3 g. (45%) of flaky crystals, m.p. 93-96°, having a blue tint. After several recrystallizations from ethanol and ethyl acetate an analytical sample, m.p. 94.0-96.2°, was obtained as colorless flakes. This compound proved to be 4-benzoylphenyl trichloroacrylate.

Anal. Calcd. for C₁₈H₉Cl₃O₃: C, 54.0; H, 2.6; Cl, 29.9. Found: C, 53.9; H, 2.5; Cl, 29.8.

In a similar way *p*-nitrophenyl trichloroacrylate, m.p. 108-109°, was obtained in 10% yield starting from *p*-nitrophenol. The colorless analytical sample, m.p. 108-109°, was obtained by crystallization from ethanol.

Anal. Calcd. for C₉H₄Cl₃NO₄: C, 36.4; H, 1.6; Cl, 35.9; N, 4.7. Found: C, 36.1; H, 1.3; Cl, 35.8; N, 4.8.

8-Benzoyl-3-chloro-6-methylflavone (IId).

A solution prepared from 11.8 g. of bromobenzene and 1.8 g. of magnesium in 60 ml. of tetrahydrofuran was added during 20 min. to a stirred solution of 10.0 g. of Id in 80 ml. of benzene. After 2 hr. at room temperature and 30 min. at reflux the tetrahydrofuran was distilled during 1 hr. and the reaction mixture was worked up as usual to yield 2.8 g. (25%) of IId, m.p. 185-187°, and 3.5 g. of unchanged Id. The analytical sample of IId, m.p. 188.4-189.4°,

was obtained by several recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{23}H_{15}ClO_3$: C, 73.7; H, 4.0; Cl, 9.5. Found: C, 73.5; H, 4.0; Cl, 9.4.

3-Chloro-2-(1-naphthyl)chromone (Ile).

An ether-benzene solution of 1-naphthylmagnesium bromide (slight excess) was added to a stirred solution of 2.15 g. of Ia in 15 ml. of benzene. After 16 hr. at room temperature the reaction mixture was treated as usual to yield a crude dark solid which was vacuum sublimed. Recrystallization from ethyl acetate yielded 2.0 g. (66%) of Ile, m.p. 223-224°, as colorless plates (I.R. band at 6.03 μ).

Anal. Calcd. for $C_{19}H_{11}ClO_2$: C, 74.4; H, 3.3; Cl, 11.6. Found: C, 74.3; H, 3.6; Cl, 11.4.

3,6-Dichloro-2-mesitylchromone (III) (III).

To a refluxing solution of 2.5 g. of Ic in 50 ml. of benzene was added 30 ml. of 0.76 N ethereal mesitylmagnesium bromide. After 21.5 hr. at reflux the mixture was worked up by treatment with ice. The solid complexes present were decomposed by stirring with 3 N hydrochloric acid. After such treatment and the usual workup no evolution of hydrogen chloride was noticed on concentration of a benzene solution of the products. The crude product was crystallized from methanol twice to yield 1.9 g. (51%) of III, m.p. 171-173° as colorless crystals (I.R. band at 6.10 μ).

Anal. Calcd. for $C_{15}H_9Cl_2O_2$: C, 64.8; H, 4.2; Cl, 21.3. Found: C, 64.8; H, 4.2; Cl, 21.2.

When an equivalent of ethylene dibromide (5) was used in the preparation of mesitylmagnesium bromide, III was not obtained in an experiment similar to the above.

3,6-Dichloro-2-(2-isopropoxy-5-methylphenyl)chromone (V).

To a solution prepared by allowing 12.65 g. of sodium to react with 250 ml. of isopropyl alcohol was added 93.5 g. of 2-bromo-4-methylphenol (12) and then 102 g. of isopropyl iodide. The stirred mixture was held at reflux for 8 hr. and then worked up as usual to yield 69 g. (60%) of 2-isopropoxy-5-methyl bromobenzene. b.p. 104-106° at 1 mm.

Anal. Calcd. for $C_{16}H_{13}OBr$: C, 52.4; H, 5.7. Found: C, 52.7; H, 5.8. About a 20% excess of 2-isopropoxy-5-methylphenylmagnesium bromide in ether was added to a solution of 20.0 g. of Ic in 80 ml. of benzene. After 18 hr. at room temperature the mixture was treated with dilute acid and the products obtained in the usual way. After two recrystallizations from ethyl acetate-Skellysolve B (petroleum ether, b.p. 65-70°) 22.7 g. (75%) of V, m.p. 134.5-135.5°, was obtained as colorless crystals (I.R. band at 6.00 μ).

Anal. Calcd. for $C_{19}H_{19}O_3Cl_2$: C, 62.8; H, 4.4; Cl, 19.5. Found: C, 62.6; H, 4.3; Cl, 19.8.

3,6-Dichloro-2-(2-hydroxy-5-methylphenyl)chromone (VI).

A solution of 3.63 g. of V in 20 ml. of acetic acid containing 3.2 g. of 48% hydrobromic acid was held at reflux for 4 hr. The solid obtained on dilution with water was recrystallized from methanol-Skellysolve B to yield 2.6 g. (81%) of VI, m.p. 215-220°. After sublimation and crystallization from methanol the analytical sample, m.p. 223-225°, was obtained as colorless crystals.

Anal. Calcd. for $C_{16}H_{13}O_3Cl_2$: C, 59.8; H, 3.1; Cl, 20.8. Found: C, 59.6; H, 2.9; Cl, 20.8.

2-Chloro-7-methyl-11H-benzofuro[3,2-b]benzopyran-11-one (VII).

To a solution of 1.35 g. of potassium *t*-butoxide in 40 ml. of *t*-butyl alcohol was added 3.21 g. of VI and the mixture was refluxed for 24 hr. The solid obtained by dilution with water was washed with cold benzene to remove a dark colored impurity and then crystallized from ethyl acetate to yield 1.5 g. (53%) of VII, m.p. 266-267° (I.R. band at 6.00 μ).

Anal. Calcd. for $C_{16}H_{13}O_3Cl$: C, 67.5; H, 3.2; Cl, 12.5. Found: C, 67.7; H, 3.3; Cl, 12.4.

3-Chlorocoumarin.

To a solution of 2 g. of Ia in 160 ml. of 50% acetic acid was added 2 g. of zinc dust. After the stirred mixture was held at 50° for 24 hr. the zinc was removed by filtration. Dilution of the filtrate yielded 1.05 g. (62%) of 3-chlorocoumarin, m.p. 121-123°. A recrystallized sample (ethanol) gave no depression in m.p. when mixed with an authentic sample (13).

4-Chloro-3-methylcoumarin.

A mixture of 4.0 g. of 4-hydroxy-3-methylcoumarin (14) and 15 ml. of phosphorus oxychloride was held at reflux for 2 hr. The dark red solution was poured on ice. The solid was collected and crystallized from ethanol (charcoal) to yield 3.5 g. (78%) of yellow crystals, m.p. 118-120°. The analytical sample, m.p. 118.4-119.6°, (I.R. band at 5.84 μ) was obtained after several recrystallizations from ethanol.

Anal. Calcd. for $C_{10}H_7O_2Cl$: C, 61.7; H, 3.7; Cl, 18.2. Found: C, 61.6; H, 3.6; Cl, 18.2.

3-Cyanoflavone.

3-Chloroflavone (IIa) was converted into 3-cyanoflavone in 58% yield by heating for 20 hr. with cuprous cyanide in *N*-methylpyrrolidone (7) at 225°. The analytical sample melted at 166-168° (I.R. band at 6.04 μ).

Anal. Calcd. for $C_{16}H_9NO_2$: C, 77.7; H, 3.7; N, 5.7. Found: C, 77.9; H, 3.6; N, 5.7.

On hydrolysis by boiling 1.5 g. of 3-cyanoflavone in 30 ml. of acetic acid containing 7.5 ml. of 48% hydrobromic acid for 3 days a mixture of solids was obtained. Crystallization from benzene-cyclohexane yielded 0.6 g. of 3-cyanoflavone. By sublimation of the remainder at 90° at 3 mm there was obtained 0.4 g. of flavone, m.p. 95.6-96.4°. A mixed m.p. with authentic flavone (8) showed no depression.

REFERENCES

- (1) The present research was supported by a grant from the U. S. Public Health Service.
- (2) Postdoctoral Fellow.
- (3) M. S. Newman and J. L. Ferrari, *Tetrahedron Letters*, 199 (1962).
- (4) M. S. Newman and S. Schiff, *J. Am. Chem. Soc.*, **81**, 2266 (1959).
- (5) D. E. Pearson, D. Cowan and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
- (6) M. S. Newman and C. Y. Peery, *ibid.*, **28**, 116 (1963).
- (7) M. S. Newman and H. Boden, *ibid.*, **26**, 2525 (1961).
- (8) T. S. Wheeler, Coll. Vol. IV, *Org. Syntheses*, p. 478, method 2.
- (9) Naming as per Chemical Abstracts. This ring system has been synthesized previously by R. Robinson and J. Walker, *J. Chem. Soc.*, 941 (1935), and by R. B. Desai and J. N. Ray, *J. Indian Chem. Soc.*, **35**, 83 (1958), but not in the same state of oxidation.
- (10) All melting points are uncorrected. The term "worked up in the usual way" means that an ether-benzene solution of the products was washed with acid and/or alkali and was then dried by filtration through a quantity of anhydrous magnesium sulfate. The solvents were then removed and the product purified by conventional methods; microanalysis by the Galbraith Laboratories, Knoxville, Tennessee.
- (11) Experiment performed by Dr. Cecile Dalton, 1963. A similar result had been obtained by Dr. Garg who carried out the condensation in tetrahydrofuranobenzene at reflux for 12 hr.
- (12) B.p. 70-72° at 2 mm, prepared by bromination of *p*-cresol in carbon tetrachloride, Th. Zincke and K. Wiederhold, *Ann.*, **320**, 199 (1902).
- (13) We thank the Dow Chemical Company, Midland, Michigan, for an authentic sample, m.p. 121.4-123.0°.
- (14) I. M. Hellbron and D. W. Hill, *J. Chem. Soc.*, 1706 (1927).

Received January 13, 1964

Columbus 10, Ohio