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ONE-STEP CONVERSION OF 3,4-DICHLOROCOUMARINS TO 3-CHLOROFLAVONES

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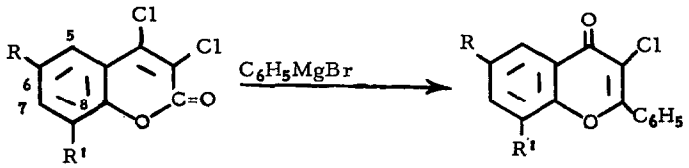
ON treatment with phenylmagnesium bromide the 3,4-dichlorocoumarins,[1] I, are converted into the corresponding 3-chloroflavones, II. This is apparently the first instance of a one-step conversion of the coumarin system into the flavone system.[2] In previous studies involving treatment of coumarins with Grignard reagents chromenes, chromenols, chromanols and benzopyrylium salts have been obtained.[3] Since the 3,4-dichlorocoumarins, I, are prepared in one step from phenols and hexachloropropene,[1] a two-step synthesis of 3-chloroflavones, II, from phenols is at hand.



Ia (R=R'=H)
b (R=CH_3, R'=H)
c (R=Cl, R'=H)
d (R=CH_3, R'=COC_6H_5)

II

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[1] M.S. Newman and S. Schiff, J. Amer. Chem. Soc. 81, 2266 (1959).

[2] F. Arndt, L. Loewe, R. Un and E. Ayca, Chem. Ber. 84, 319 (1951), have shown that 4-hydroxycoumarins are in tautomeric equilibrium with 2-hydroxy chromones. However, we know of no case in which a coumarin is directly converted into a flavone.

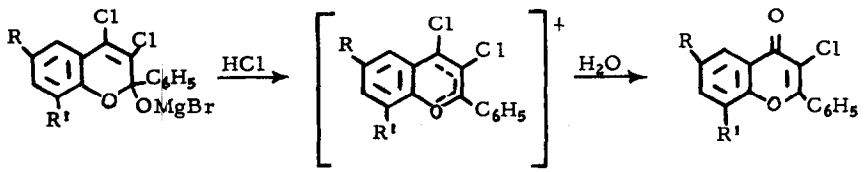
[3] For reviews see S.M. Sethna and N.M. Shah, Chem. Rev. 36, 1 (1945); R.C. Elderfield, Heterocyclic Compounds Vol. II, p. 173. John Wiley, New York (1951).

On addition of a small excess of ethereal phenylmagnesium bromide to solutions of Ia, Ib, Ic and Id in benzene, the following compounds were obtained: IIa (75% yield), m.p. 121.8-123.2°; IIb (70% yield), m.p. 196.0-197.2°; IIc (52% yield), m.p. 135.0-136.6°; and IId (25% yield), m.p. 188.4-189.4°.

The requisite 8-benzoyl-3,4-dichloro-6-methylcoumarin, Id, was prepared in 90% yield by reaction of 2-hydroxy-5-methylbenzophenone in nitroethane with hexachloropropene and aluminum chloride. This variant of the original[1] 3,4-dichlorocoumarin synthesis was suggested by the high yields obtained on condensations of o-hydroxybenzophenones with benzotrichlorides to yield 2,6-dibenzoylphenols.[4] Further studies in this area are underway.

The structure of IIa was established by chlorination of flavanone to 3-chloroflavone[5] which proved to be identical to IIa. In addition, treatment of IIa with cuprous cyanide in n-methylpyrrolidone[6] yielded 3-cyanoflavone, m.p. 166.8-168.2°. Hydrolysis of this nitrile in hot acetic acid yielded flavone, m.p. 96-97°, identical to an authentic sample prepared as described.[7]

The conversion of 3,4-dichlorocoumarins, I, to 3-chloroflavones, II, probably proceeds as follows.



III II

[4] M.S. Newman and A.G. Pinkus, J. Org. Chem. 19, 992 (1954).

[5] H. de Diesbach and H. Kramer, Helv. Chim. Acta 28, 1399 (1945).report that bromination of flavanone yields 3-bromoflavone.

[6] M.S. Newman and H. Boden, J. Org. Chem. 25, 2525 (1961).

[7] A. Loewenbein, Ber. Dtsch. Chem. Ges. 57, 1515 (1924).

The key intermediate is probably the benzopyrylium salt, III, which is attacked by water at the 4-position to yield the 3-chloroflavone, II. We hope to explore the general behavior of β-chloroethylenic ketones and esters with Grignard reagents as useful synthetic transformations appear likely.

In conclusion, we wish to express our thanks for support of this work to the U.S. Public Health Service (RG-7450).