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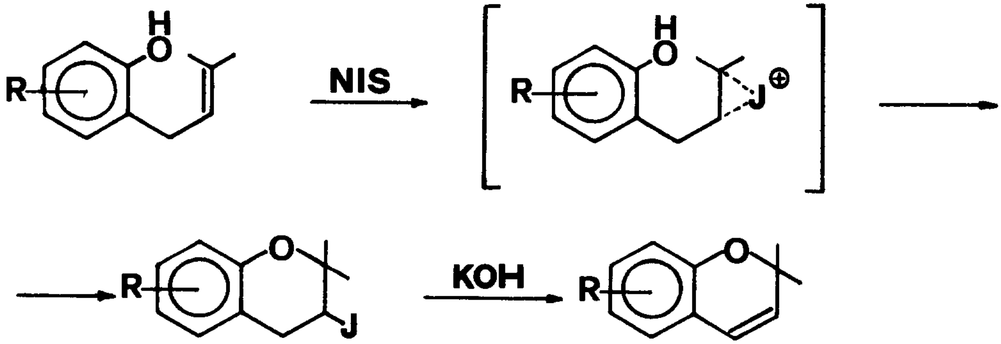
A NEW SYNTHESIS OF 2,2'-DIALKYLCHROM-3-ENES AND FLAV-3-ENES

Alessandro Bongini, Giuliana Cardillo, Mario Orena, Gianni Porzi and Sergio Sandri
Istituto Chimico " G. Ciamician " , Università di Bologna
Via Selmi 2 - 40126 Bologna, ITALY

Abstract. N-iodosuccinimide (NIS) induces cyclization of substituted 2-allylphenols to 3-iodochromanes which may be dehydrohalogenated to the corresponding chrom-3-enes.

Almost every class of natural phenolic compounds contains examples of substances with 2,2'-dialkylchromene rings [1]. Recently Pratt and Bowers [2] found that chromene derivatives, Precocene I and II, extracted from the plant Ageratum houstonianum, have " antijuvenile hormone " effects. The discovery of these new natural insecticides prompted interest in the development of new syntheses of chrom-3-enes [3a,b], as alternatives to the well known DDQ oxidation [4a,b].

The key step of the synthesis we report here is based on the intramolecular ring closure allowed by activation of an olefinic double bond by means of an iodonium intermediate. While the usual conditions reported for the iodolactonization [5] have been found to promote the aromatic ring iodination, especially for activated phenols, N-iodosuccinimide (NIS) has been shown [6a,b] to be a convenient and practical reagent to provide positive iodine.



The reaction was carried out in an aprotic solvent such as CH_2Cl_2 and under particularly mild conditions. The reaction temperature was found to be very critical in order to obtain a good yield, the optimum being around 30°: at higher temperatures ring iodination was favoured. The yields in 3-iododerivatives are reported in the Table and are generally good in the cases considered. The yields are lower for 3-iodo-7-methoxy-2,2'-dimethylchromane 5, the key intermediate to Precocene I 6, since the $-OCH_3$ activation allows a competitive ring iodination. The reaction of 2-allyl-4-methylphenol 13 with N-iodosuccinimide did not give the double bond addition, but the aromatic iodination product was obtained in 90% yield [7].

The iododerivatives were then converted into the corresponding 3,4-unsaturated compounds by treatment with 10% methanolic potassium hydroxide solution in very good yield [8].

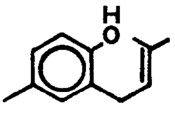
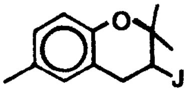
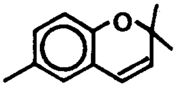
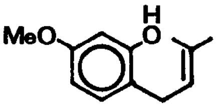
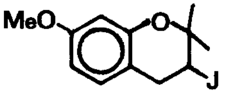
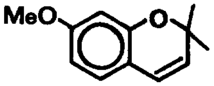
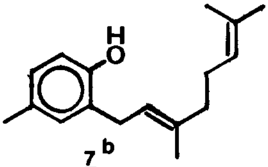
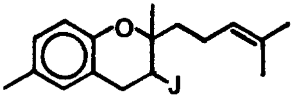
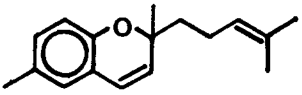
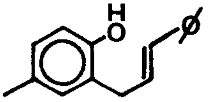
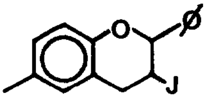
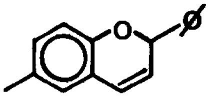
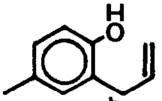
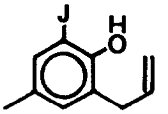
Although N-bromosuccinimmide is known to introduce selectively bromine in the allylic position, this reagent has also been described as a source of bromonium ion [9], when used in a polar solvent. Therefore we tested N-bromosuccinimide to cyclofunctionalize the allyl-substituted phenols utilizing t-BuOH as a solvent [10]. By treating 2-(3-methylbut-2-en-1-yl)-4-methylphenol 1 in t-BuOH at 35° for 2 h, the 3-bromochromane was obtained in 75% yield. NMR (CCl_4) spectrum showed signals at δ values of 1.3 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.15 (d, 2H, CH_2; J = 7 Hz), 4.1 (dd, 1H, CHBr; J = 7 Hz) and 6.4 - 7 (m, $3H_{arom}$). Elimination of HBr was carried out in 10% KOH methanolic solution and chrom-3-ene 3 was obtained practically in quantitative yield. In contrast, an attempt to prepare Precocene I by the same method, starting from 4, led to the 4-bromoderivative in 90% yield.

Typical experimental procedure

3-iodo-2,2',6-trimethylchromane 2

N-iodosuccinimide (500 mg; 2.2 mmol) was added to a magnetically stirred solution of 2-(3-methylbut-2-en-1-yl)-4-methylphenol 1 (380 mg; 2 mmol) in 10 ml CH_2Cl_2, protected from light. After 1 h at 30° the solution was diluted with ether and water and extracted with ether. The organic layer was washed with $Na_2S_2O_3$ solution, dried (Na_2SO_4) and evaporated. After chromatography on silica gel by eluting with hexane, 2 was obtained as an oil in 90% yield. NMR (CCl_4) spectrum gave δ values of 1.41 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.38 (d, 2H, CH_2; J = 10 Hz), 4.36 (dd, 1H, CHJ; J = 10 Hz) and 6.5 - 7.2 (m, $3H_{arom}$).

TABLE - Reaction of allyl phenols with NIS. Preparation of chrom-3-enes and flav-3-enes.

Phenol	Iododerivative	Yield[a] (%)	Chrom-3-enes or flav-3-enes	Yield[a] (%)
 1[b]	 2	90	 3	95
 4[b]	 5	67	 6	82
 7[b]	 8	85	 9	83
 10[c]	 11[d]	45	 12	90
 13[b]	 14[e]	90		

(a) Yields refer to pure isolated compounds purified by silica gel chromatography using hexane as eluent; all the products were identical in all respects with authentic material. (b) 1, 4, 7 and 13 were prepared from sodium phenolates in refluxing benzene with allylic bromides [11]. (c) 10 was obtained from p-cresol and cinnamyl alcohol in formic acid [12]. (d) Compound 11 shows in the NMR spectrum (CCl_4) characteristic signals at 4.5 (dt, 1H, CHJ; J = 10 Hz) and 5.1 δ (d, 1H, CHJ-CHPh-O-; J = 10 Hz). (e) Compound 14 shows in the NMR spectrum (CCl_4) characteristic signals at 6.8 (d, 1H, H_3 aromatic ring; J = 3 Hz), 7.25 δ (d, 1H, H_5 aromatic ring; J = 3 Hz).

2,2',6-trimethylchrom-3-ene 3

Compound 2 (634 mg; 2 mmol) was treated with 10% methanolic potassium hydroxide solution (10 ml) at 50° for 2 h. After usual work-up, the organic layer was evaporated in vacuo and 3 was recovered in 95% yield after silica gel chromatography, by eluting with hexane. NMR (CCl_4) spectrum gave δ values of 1.38 (s, 6H, CH_3), 2.2 (s, 3H, CH_3), 5.45 (d, 1H, C$\underline{H}$=CH-Ph; J = 10 Hz), 6.2 (d, 1H, CH=C$\underline{H}$-Ph; J = 10 Hz) and 6.45 - 7.1 (m, $3H_{arom}$).

REFERENCES

1) L. Merlini, in " Advances in Heterocyclic Chemistry " , Vol. 18, 1975, Academic Press, N.Y., pag. 159.
2) G.E. Pratt and W.S. Bowers, Nature, 265, 548 (1977).
3) (a) W.S. Bowers, T. Ohta, J.S. Cleen and P.A. Marsella, Science, 193, 542 (1974);
(b) D.L.J. Clive, G. Chittattu, N.J. Curtis, W.A. Kiel and C.K. Wong, J.C.S., Chem. Comm., 725 (1977).
4) (a) G. Cardillo, R. Cricchio and L. Merlini, Tetrahedron, 24, 4825 (1968);
(b) G. Cardillo, R. Cricchio and L. Merlini, Tetrahedron Lett., 907 (1969).
5) J. Klein, J. Amer. Chem. Soc., 81, 3611 (1971).
6) (a) C. Djerassi and K.T. Lenk, J. Amer. Chem. Soc., 75, 3494 (1957);
(b) M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro and L. Mangoni, Tetrahedron Lett., 3661 (1976).
7) J.W. Lown and A.V. Joshua, Can. J. Chem., 55, 122 (1977).
8) G. Descotes and D. Missos, Synthesis, 149 (1971).
9) C.O. Guss and R. Rosenthal, J. Amer. Chem. Soc., 77, 2549 (1955).
10) A. Bresson, G. Dauphin, J.M. Geneste, A. Kergomard et A. Lacourt, Bull. Soc. Chim. Fr., 2432 (1970).
11) J. Hlubucek, E. Ritchie and W.C. Taylor, Austral. J. Chem., 24, 2355 (1971).
12) L. Jurd, Tetrahedron, 25, 1407 (1969).
13) M. Sliwa, H. Sliwa et P. Maitte, Bull. Soc. Chim. Fr., 958 (1974).

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