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FRIEDEL-CRAFTS REACTION OF 3,6-DIHYDRO-4-METHYL-2H-PYRAN WITH PHENOLS. A CONVENIENT SYNTHESIS OF A KEY INTERMEDIATE OF ALPHA-TOCOPHEROL

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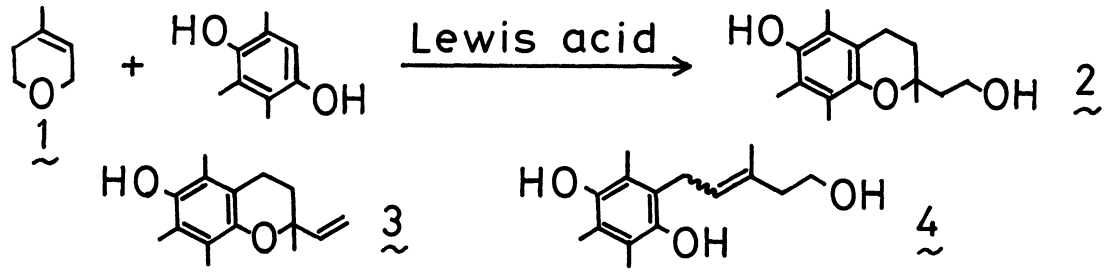
The Friedel-Crafts reaction of 3,6-dihydro-4-methyl-2H-pyran with 2,3,5-trimethylhydroquinone afforded 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-ethanol in good yield.

In the course of our investigation to utilize 3,6-dihydro-4-methyl-2H-pyran (1)[1] as a building block for terpenoid skeleton construction, attention was focused to a convenient synthesis of chroman derivative (2) which has been shown to be useful not only as a key intermediate of natural alpha-tocopherol[2] but also as a raw material of various type of antioxidants.[3]



Into a mixture of 2,3,5-trimethylhydroquinone (453 g; 3 mol), powdered anhydrous aluminum chloride (400 g; 3 mol), and 1,2-dichloroethane (3 l), 1 (353 g; 3.6 mol) was added dropwise during 1 h at room temperature. After refluxing for 15 min, the reaction mixture was poured into ice-water and stood overnight. A pale green precipitate thus obtained was filtered off, washed with cold ether, and dried under reduced pressure to obtain 2[4] in 68-71% yields. Extraction of the mother liquor with ether revealed the formation of 3[4] (ca. 10%) and a trace amount of 4[4] as by-products. The use of zinc chloride, ferric chloride or boron

trifluoride etherate, instead of aluminum chloride, afforded 2 in 5, 30, and 81% yields respectively (determined by GC analyses). Similar reactions of 1 with p-chlorophenol or p-cresol gave the corresponding chroman-2-ethanols[4] in ca. 60% isolated yield. But, in the case of resorcinol or hydroquinone, the yields of chroman-2-ethanols[4] were no more than 15% owing to the concurrent formation of dialkylated products.

As a convenient and effective method for optical resolution of 2 has recently been established by using diastereomeric diesters of 2,[5] our present process to afford 2 comes to be one of the simplest and practical way to natural alpha-tocopherol and tocotrienol.

References

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M. Horner and A. Nissen, Japan Kokai Patent, 145282 (1981), U.S. Patent, 4344886 (1982); Chem. Abstr., 96, 35092 (1982).

3) M. Horner and G. Teege, Japan Kokai Patent, 146768 (1982), U.S. Patent 4374258 (1983); Chem. Abstr., 98, 4474 (1983).
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4) Physical data are as follows.
2: mp 152-153 °C, bp 153-163 °C/12 Pa, ^{1}H NMR δ 1.2 (s, 3H), 1.6-2.3 (m, 13H), 2.57 (t, J=7 Hz, 2H), 3.85 (t, J=7 Hz, 2H), 4.0 (br.s, 2H);
3: FD-MS $[M]^+$ 232; 4: FD-MS $[M]^+$ 250; 2-(6-chloro-3,4-dihydro-2-methyl-2H-1-benzopyran-2-ethanol: bp 155 °C/400 Pa; 2-(3,4-dihydro-2,6-dimethyl-2H-1-benzopyran-2-ethanol: bp 145 °C/400 Pa; 2-(3,4-dihydro-7-hydroxy-2-methyl-2H-1-benzopyran-2-ethanol: mp 101-102 °C; 2-(3,4-dihydro-6-hydroxy-2-methyl-2H-1-benzopyran-2-ethanol: mp 78.5-80.5 °C

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