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Novel Oxidation of Homoallylic Sterols with Pyridinium Dichromate*

重铬酸吡啶盐作用下烯丙基甾醇的氧化反应研究

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Abstract Stigmasterol was oxidized with pyridinium dichromate. Stigmast-4, 22-dien-6β-ol-3-one and stigmast-4, 22-dien-3, 6-dione were obtained as main product separately in different reactive conditions. The result was different from the report in the related literature.

Key words homoallylic sterols, pyridinium dichromate (PDC), stigmast-4, 22-dien-6β-ol-3-one, stigmast-4, 22-dien-3, 6-dione

摘要 在不同的反应条件下,用重铬酸吡啶盐 (PDC) 氧化豆甾醇,分别得到以豆甾-4, 22-二烯-6β-羟基-3-酮或豆甾-4, 22-二烯-3, 6-二酮为主的产物。结果与有关文献的报道有所不同。

关键词 烯丙基甾醇 重铬酸吡啶盐 (PDC) 豆甾-4, 22-二烯-6β-羟基-3-酮 豆甾-4, 22-二烯-3, 6-二酮
中图法分类号 O627.51

Many spontaneous hydroxylated sterols have potent cytotoxicity[1~3]. In our study, the synthesis of hydroxylated sterols, namely Nephthalsterols A and B[3], stigmast-4, 22-dien-3, 6-dione was designed for a synthetic intermediate. Referring to Scettri's method[4], stigmast-4, 22-dien-3, 6-dione may be obtained when stigmasterol was oxidized with pyridinium dichromate (PDC) (3 equiv.) in DMF under 80℃. To our surprise, a 6-hydroxyl compound, stigmast-4, 22-dien-6β-ol-3-one was obtained as main product instead of the desired product, stigmast-4, 22-dien-3, 6-dione. The structure of stigmast-4, 22-dien-6β-ol-3-one was proved by IR and NMR data. This result was different from the Scettri's report (Fig. 1).

However, when the amount of PDC increased from 3 equiv. to 6 equiv., the main product of the reaction was stigmast-4, 22-dien-3, 6-dione. This is consistent with the R. W. Hartmann's result[5]. For confirming this result, pregn-5-en-3β-20-one was also oxidized with PDC (3 equiv.) under the same conditions. A 6-hydroxylated sterol, but not a 6-keto-compound was obtained as well. This experiment supports the results mentioned above (Fig. 2.).

In order to prepare stigmast-4, 22-dien-3, 6-dione, CH_2Cl_2 was used as solvent. The stigmasterol was oxidized smoothly with PDC at room temperature and the target compound, stigmast-4, 22-dien-3, 6-dione, was yielded as high as 64%. Alternatively, when pyridinium chlorochromate (PCC) was used as oxidative agent in CH_2Cl_2 at 10℃~ 15℃[6], stigmast-4, 22-dien-3, 6-dione was yielded up to 83%.

1 Experimental Section

Stigmasterol and pregn-5-en-3β-20-one were obtained from the Merck Co.. PDC was prepared according to the reference[7] and PCC was prepared according to the reference[8]. Melting points were determined on a X_4 apparatus and uncorrected. Infrared spectra were measured with a Nicolet 205 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a

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JEOL FX-90Q (90 MHz) and a Unity Inova 500 (500MHz) spectrometer in $CDCl_3$, using tetramethylsilane (TMS) as internal standard.

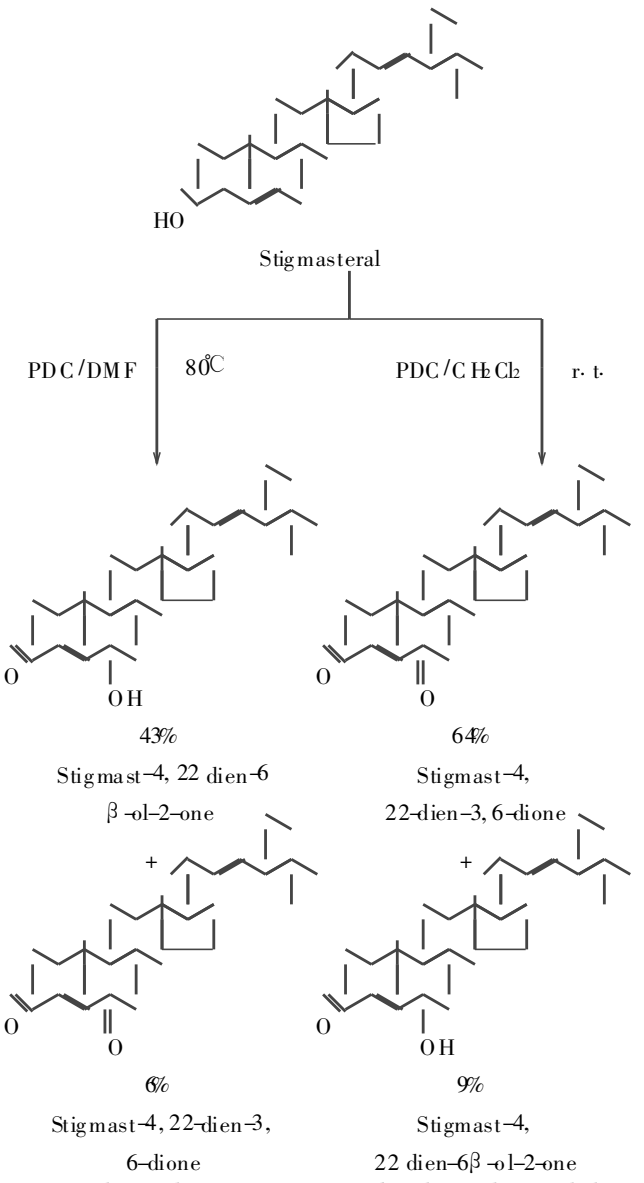

Fig. 1 The oxidation of stigmasterol with pyridinium dichromate

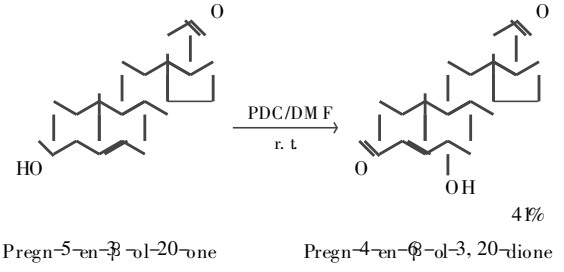

Fig. 2 The oxidation of 3β-hydroxy△5-pregnen-20-one with pyridinium dichromate

2 General Procedure for PDC Oxidation

To a solution of homoallylic hydroxy steroid (1.2 mmol) in dimethylformamide (10 ml) was added PDC (3.6 m mole) in one portion. The reaction mixture was stirred at 80℃ for 15 h. The mixture was poured into ethyl acetate (30 ml) and the resulting brown granular solid was filtered with filter paper and washed with warm ethyl acetate (5× 15 ml). The organic phase was washed with water (3× 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure at 45℃. The residue was chromatographed on silica gel using petroleum (60℃~ 90℃): acetone (3 1) as eluent.

3 Results

Stigmast-4, 22-dien-6β-ol-3-one Oxidation of Stigmasteral (0.50 g, 1.2 mmol) in DMF (10 ml) with PDC (1.36 g, 3.6 mmol) gave stigmast-4, 22-dien-3, 6-dione (30 mg) (6% yield) and stigmast-4, 22-dien-6β-ol-3-one (220 mg) (43% yield): M. p. 175℃~ 176℃. IR (KBr): 3409, 2952, 1679, 1039, 969, 835 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.763 (3H, s, 18-CH_3), 0.802 (3H, d, J= 5.1, 26- or 27-CH_3), 0.849 (6H, d, J= 5.1, 26- or 27-CH_3), 0.808 (3H, t, J= 6.9, 29-CH_3), 1.026 (3H, d, J= 6.6, 21-CH_3), 1.381 (3H, s, 19-CH_3), 4.348 (1H, d, J= 2.0Hz, 6α-H), 5.037 (1H, dd, J= 15.0Hz, J= 9.0Hz, 22-H), 5.153 (1H, dd, J= 15.0Hz, J= 8.8Hz, 23-H), 5.817 (1H, s, 4-H).

Oxidation of stigmasterol (210 mg, 0.5mmol) in CH_2Cl_2 (6 ml) with PDC (570 mg, 1.5 mmol) under r. t. for 30 h gave stigmast-4, 22-dien-6β-ol-3-one (20 mg, 9% yield) and stigmast-4, 22-dien-3, 6-dione (140 mg, 64% yield).

Pregn-4-en-6β-ol-3, 20-dione Oxidation of pregn-5-en-3β-ol-20-one (370 mg, 1.2 mmol) in DMF (10 ml) with PDC (1.36g, 3.6 mmol) gave pregn-4-en-6β-ol-3, 20-dione (160 mg) in 41% yield: M. p. 178℃~ 179℃. IR (KBr): 3423, 2938, 1700, 1665, 1046, 835 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 0.70 (3H, s, 18-CH_3), 1.38 (3H, s, 19-CH_3), 2.13 (3H, s, 21-CH_3), 4.36 (1H, m, 6α-H), 5.81 (1H, s, 4-H).

Stigmast-4, 22-dien-3, 6-dione. Oxidation of stigmasterol (500 mg, 1.2 mmol) in dried CH_2Cl_2 (10 ml) with PCC (1.30g, 6 m mole) for 29 h at 10℃~ 15℃ gave, after silica gel column chromatography (eluent, petroleum (60℃~ 90℃): acetone= 3 1),

stigmast-4, 22-dien-3, 6-dione(430 mg) in 83% yield: M. p. 134℃ ~ 135℃. IR (KBr): 2959, 1714, 1686, 1609, 969, 864 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.743 (3H, s, 18-CH_3), 0.805 (3H, t, J= 7.0, 29-CH_3), 0.798 (3H, d, J= 6.5, 26- or 27-CH_3), 0.849 (3H, d, J= 6.5, 26- or 27-CH_3), 1.036 (3H, d, J= 7.0, 21-CH_3), 1.169 (3H, s, 19-CH_3), 5.040 (1H, dd, J= 15.2, J= 9.0, 22-H), 5.150 (1H, dd, J= 15.2, J= 8.5, 23-H), 6.171 (1H, s, 4-H).

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量将水抽干, 于110℃烘12 h, 磨匀后装柱进行柱层析。用这种处理过的硅胶我们成功地分离出产物(**2**)。

IR (cm^{-1}, 液膜): 3064 (ν_{Ar-H}), 1720 ($\nu_{C=O}$), 1641 ($\nu_{C=N}$), 751, 691 (苯环)。

^1H-NMR ($CDCl_3$, δ): 1.28 (t, *J* = 7.40, 6.72, 3H, $-CH_3$), 1.33 (dd, *J* = 7.40, 8.16, 2H), 1.69 (dd, *J* = 7.40, 7.36, 2H), 4.21 (q, *J* = 7.40, 2H, OCH_2-), 7.57 (m, 5H, Ph), 8.38 (s, 1H, CH=N)。

3 结论

将MWI和PTC技术相结合, 在无溶剂条件下, 迅速 (1 min) 实现了醛亚胺与1, 2-二溴乙烷的串联烷基化反应。与传统加热方法相比, 显著缩短了反应时间, 大大提高了反应效率, 操作简单, 后处理方便, 三废少, 符合节能、清洁生产、绿色合成的要求, 应用前景广阔。

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