Content variation of disubstituted adamantane in a synthetic procedure to adapalene

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ABSTRACT

Content variation of disubstituted adamantane was reported. Disubstituted adamantane was formed through an unusual Friedel-Crafts reaction of adamantanol with 4-bromoanisole. The structure of it was identified by means of an X-ray crystal structure determination.

Keywords: Adapalene, disubstituted adamantane, friedel-crafts alkylation.

INTRODUCTION

Retinoids, natural and synthetic analogues of retinoic acid, an active metabolite of vitamin A, play a major role in controlling cell proliferation, differentiation and morphogenesis [1-2]. These properties offer this class of substances a high potential for their chemopreventive and therapeutic application in the areas of oncology and dermatology [3-5]. Some synthetic retinoids, such as compound 1 (adapalene) have been proven to be clinically useful in the treatment of acne and psoriasis [6-9] and since 1996 it has been used as a topical drug under the trade name of Differin [10-12].

Recently, we were involved in the optimization of the synthesis sequence of adapalene, according to the procedures (Scheme 1) [13-14].
The known synthetic methods capable of producing compound 1 employ 1-adamantanol as the starting material. It generates monosubstituted adamantane (5) as main product through Friedel-Crafts Alkylation. We found this process also generated disubstituted adamantane (9) as by-product. Synthesis of disubstituted adamantane is outlined in Scheme 2. First, a Friedel-Crafts alkylation with 1-adamantanol (3) and 4-bromophenol (4) led to compounds 5 and 9. Then, compounds 5 and 9 were converted into compounds 6 and 2 through methylation by iodomethane or dimethyl sulfate. Finally, compound 2 was isolated and characterized by NMR and X-ray crystal structure determination (Figure 1). After fine-tuning the process, the disubstitute adamantane become the major product.

![Scheme 2](image)

**Figure 1 Perspective view of the X-ray structure of compound 2**

We were very surprised by the results and a search in the literatures showed that compound 2 has been isolated as an unexpected impurity by E. Brenna in 2007 [15]. But the percentage of compound 2 versus compound 6 in the crude product and the influence factors of their content variations had not been reported, which were strictly related to the purity of compound 6. In this paper, the content variations of compound 2 in different conditions and the suggested mechanism had been discussed.

**EXPERIMENTAL SECTION**

2.1 X-ray Crystallographic Analysis

A crystal of the compound 2 (colorless, plate-shaped, size 0.20 x 0.10 x 0.06 mm) was mounted on a glass fiber
with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data
collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo K
radiation (λ = 0.71073 Å), operating at 50 kV and 30 mA over 2 ranges of 3.90 - 49.96°. No significant decay was
observed during the data collection. Data were processed on a PC using the Bruker AXS Crystal Structure Analysis
Package [16].

2.2 1HNMR spectroscopy

1HNMR spectra were acquired on a Bruker DMX 300 instrument at 305 K. The hydrogen chemical shifts is referred
to the internal tetramethylsilane(TMS). The coupling constants are expressed in Hertz.

2.3 HPLC

HPLC analyses were performed on an Agilent 1100 liquid chromatograph instrument, using a Agilent C18 column
(4.6 mm ×150 nm).

2.4 Chemistry

A typical synthetic procedure of compound 9:

3 (3.05 g, 0.020 mol) and 4 (3.46 g, 0.020 mol) were dissolved in CH2Cl2 (18 mL). To the resulting solution was
slowly added the concentrated H2SO4 (1.07 mL 0.020 mol) with internal temperature at around 25-30 °C. The
resulting mixture was stirred at around 30 °C for 3 hours, poured into water (100 ml), neutralized to pH 6 with
saturated sodium carbonate solution, extracted with CH2Cl2 (3×100 mL). The organic phase was washed with water
(2 x 100 ml), dried over anhydrous sodium sulfate, filtered. HPLC showed the solution contained about 30%
compound 9, 70% compound 5. The solution was evaporated to dryness. The solid was purified by flash
chromatography, eluted with the mixture of CH2Cl2 and methanol (95 : 5) to give 3.62 g pure light yellow solid
compound 9 (99.5 % HPLC). Yield: 37.5%. The compound also can be obtained by recrystallizing the crude solid in
chloroform and isooctane. The recovery was lower. 1H NMR (CDCl3, 400 MHz): 7.33 (s, 1H), 7.18 (d, 1H),  6.55 (d,
1H), 4.81 (s, 1H), 2.42 (s, 1H), 2.30 (s, 1H), 2.19 (d, 2H), 2.05 (d, 2H), 1.79 (s, 1H).

A typical synthetic procedure of compound 2:

Dimethyl sulfate (2.0 mL, 0.021 mol) was added to a suspension of compound 9 (4.78 g, 0.010 mol) and anhydrous
potassium carbonate (6.61 g, 0.063 mol) in dry acetone (100 mL). The mixture was reflux overnight, poured into
water (200 ml), extracted with CH2Cl2 (2 × 100 mL). The organic layer was washed with 1 M NaOH (2×100 mL)
and brine (2×100 mL), dried over anhydrous sodium sulfate, filtered. To the filtrate was added heptane  (200 mL)
dried over anhydrous sodium sulfate, filtered. The resulting solution was concentrated. Off-white solid came out during c oncentration. The solid was filtered, washed with heptane to

RESULTS AND DISCUSSION

The formation of compound 9 was not reported in the original synthesis of compound 1 [13-14]. It was possibly
because compound 9 and 5 have similar polarity and close NMR spectrum. By following the exact procedure in the
reference [13], about 5 % compound 9 was detected in the reaction by carefully developed HPLC and TLC methods.
The recrystallization of the crude in isooctane cannot remove compound 9. On the contrary the solid came out from
the solution enriched compound 9 due to its poorer solubility in isooctane. The percentage of compound 9 versus
compound 5 in the crude product was increased with increased reaction temperature (5, 10, 20, 30 °C) while using
either CH2Cl2 or CHCl3 as solvents. But when using chloroform as solvent the percentage of compound 9 versus
compound 5 was decreased with elevated addition temperature (40, 50, 60 °C) of sulfuric acid (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Substrate: Comp. 3 versus Comp. 4</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Yield of Comp. 9 (%)</th>
<th>Yield of Comp. 5 (%)</th>
<th>Resultant: Comp. 9 versus Comp. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>5</td>
<td>CH2Cl2</td>
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<td>20.2</td>
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<tr>
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<td>60</td>
<td>CHCl3</td>
<td>17.9</td>
<td>19.6</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Liu et al reported an improved method for the synthesis of adapalene [14]. They reported quantitative yield for
synthesis of compound 5 by adding solution of concentrated sulfuric acid in glacial acetic acid. We found that this
method also generated compound 9. At 5 °C, the crude compound continued about 3 % compound 9. It was
increased to about 5 % at 25 °C.

Mechanism for the formation of compound 9 is not difficult to understand according to the early studies of solvolysis inductive, hyperconjugative effects for 1-adamantyl cation by Sunko and Grob [17-19]. Adamantanol forms stable adamantyl cation (scheme-3) and reacts with 4-bromophenol to give mono-substituted compound 5 (scheme-3). This compound is the major product at low temperature. Due to the inductive effect of phenol, compound 5 can regain the charge from another adamantyl cation. This cation is more stable than the original adamantyl cation. This new cation can further react with 4-bromophenol and forms disubstituted compound 9. Due to its poor solubility, compound 9 precipitated out from reaction. No trisunstituted or tetrasubstituted compound was observed. This mechanism was supported by the observation of adamantane in the reaction detected by GC and relatively low yield. The yield of disubstituted compound was increased between reaction temperature of 5 to 30 °C. This may attribute to the increased exchange rate of product 5 and adamantyl cation. But the yield started to decrease with even higher temperature may indicate faster reaction rate of adamantyl cation and 4-bromophenol versus cation exchange rate.

CONCLUSION

Compound 9 was formed during Friedel-Crafts step employed to prepare intermediate 5. The structure of its methylated derivative, compound 2, was identified by means of an X-ray crystal structure determination. The percentage of compound 9 versus compound 5 in the crude product and the influence factors of their content variations had been reported, which were strictly related to the purity of compound 5. Furthermore, the suggested mechanism had been discussed.

REFERENCES

Crystal data for 2 at 180 K. C24H26Br2O2, M = 506.27. Monoclinic, space group C2, a = 21.157(4), b = 7.4207(14),
c = 6.6781(13) Å, β = 99.052(2)°, V = 1035.4(3) Å³, F(000) = 512, Dc(Z=2) = 1.624 g cm⁻³, μ(Mo Kα) = 0.95 cm⁻¹, crystal
dimension 0.20x0.10x0.06 mm, 2θ max = 50°, wR(all 4823 data) = 0.0832, conventional R (1761 data with I>2σ(I)) = 0.0409. Complete crystallographic data, as a CIF file, has been deposited with the Cambridge Crystallographic Data Centre (CCDC No.638605). Copies can be obtained free of charge from: The director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk)