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An Unusual Formation of Cyclic Sulfite at C-4 and C-5 Positions of Taxane

Meng ZHANG, Da Li YIN*, Ji Yu GUO, Xiao Tian LIANG

Institute of Materia Medica, Chinese Academy of Medical Science &
Peking Union Medical College, Beijing 100050

Abstract: An unusual formation of cyclic sulfite at C-4 and C-5 positions of taxane was accomplished by treatment of compound **1** with excess $MeSO_2Cl/Et_3N$ and a possible mechanism was proposed.

Keywords: Paclitaxel, taxane, mesylation.

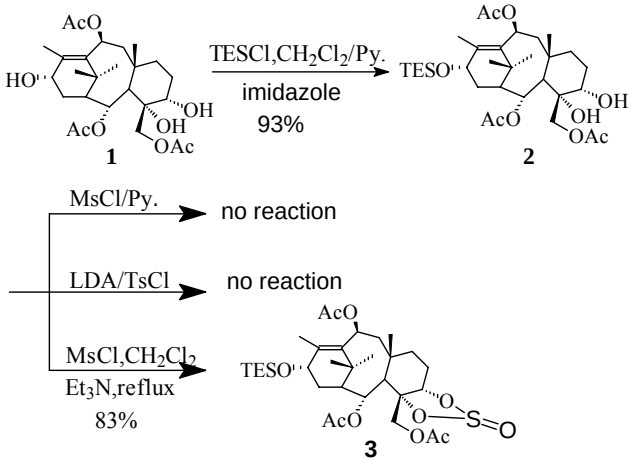
We have recently reported the synthetic studies of 1, 7, 9-trideoxypaclitaxel[1] which is a possible anticancer agent based on analysis of the structure-activity relationship (SAR). Several reactions were found to give exciting results[1,2]. Here we will discuss an unusual formation of a cyclic sulfite. Compound **1**[1] was protected with TES group at C-13 hydroxyl to form **2** which was treated with $MeSO_2Cl$/pyridine or TsCl/LDA[3] to introduce a sulfonyl group at C-5 position. But no reaction happened. When excess $MeSO_2Cl/Et_3N$ was used to treat **2**, an unidentified compound was obtained[4]. Entry of the S=O group was deduced from its molecular formula $C_{32}H_{52}O_{10}SSi$, established from HRFAB MS *m/z* $[M+Na]^+$ 679.2932 (calcd 679.2942). ^1H NMR shows that, compared with **2**, the proton signal at C-5 position was obviously moved from 3.86 ppm to 5.22 ppm, which means the S=O group was linked with C-5-OH. We thought the possible structure of the obtained compound was compound **3**. To prove this structure, we treated compound **2** with $SOCl_2$ to generate compound **3**. ^1H NMR shows compound **3** has the same proton signals as the unknown compound. Now we are sure that compound **3** has been obtained in the reaction system of excess $MeSO_2Cl/Et_3N$.

At the beginning we wondered that a little $SOCl_2$ might exisit in the solution of $MeSO_2Cl$. The aqueous solution of I_2/KI was employed to check the concealed $SOCl_2$. The result showed no $SOCl_2$ was contained in the solution of $MeSO_2Cl$. Treatment of **2** with excess $MeSO_2Cl$/pyridine had no reaction, which also indicated $SOCl_2$ did not exist

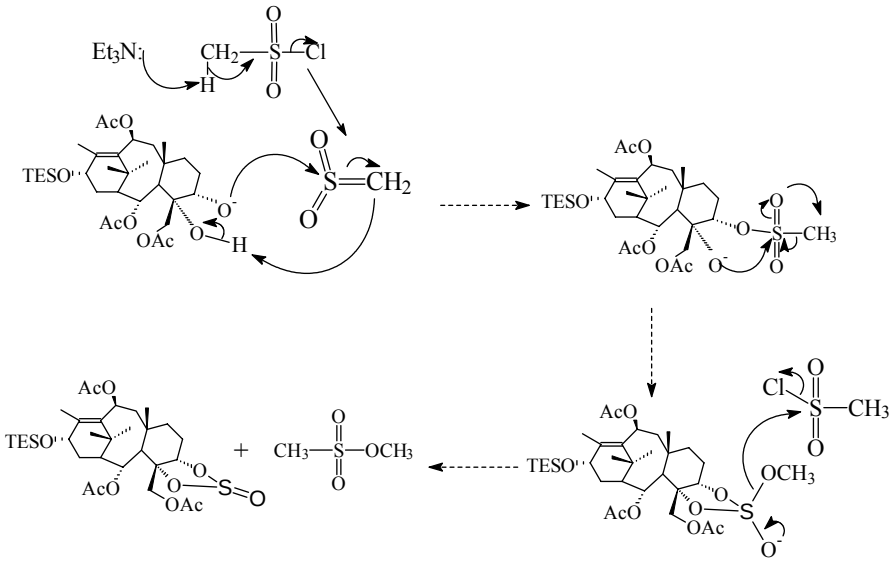
* E-mail: yindali@imm.ac.cn

in the solution of $MeSO_2Cl$. How to form the compound **3** under this reaction condition is an interesting question. Molecular simulation of the optimized structure of **2** showed that, like taxol, compound **2** has an upside-down cup shape. TES group lies below the ring face and the methyl of the TES group is very close to the hydroxyl of C-4 and C-5, which made $MeSO_2Cl$ very difficult to approach C-5 hydroxyl. Thus $MeSO_2Cl$/pyridine and TsCl/LDA cannot react with compound **2**. The excess $MeSO_2Cl/Et_3N$ can react with compound **2** because a sulfene intermediate was involved in the process of cyclic sulfite formation. A possible mechanism was proposed in **Scheme 2**. Et_3N, as a strong base, can catch a proton from $MeSO_2Cl$ to form the active sulfene molecule[5]. The pla-

Scheme 1



Scheme 2



ne-shaped sulfene makes it easier to approach the C-5 hydroxyl. Usually the C-4 hydroxyl group which lies below the reversal cup-shape face is very difficult to be attacked by organic base. But the anion of methane of sulfonyl which was formed from C-5-oxy attack is very close to C-4 hydroxyl and catches the hydrogen of C-5 hydroxyl. The C-S bond was broken up owing to oxygen anion attack. The formed methoxyl group was removed by a formation of sulfonyl ester.

In summary, an unusual formation of a cyclic sulfite have been found and a possible mechanism involved sulfene intermediate have been proposed.

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References and Notes

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4. Spectral data of compound **2**: colorless film; FABMS *m/z* 633 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$, δppm) 6.05 (dd, 1H, *J* = 10.7 Hz, 5.7 Hz, H-10), 5.38 (d, 1H, *J* = 3.9 Hz, H-2), 4.49 (br.dd, 1H, H-13), 4.47 (d, 1H, *J* = 12.6 Hz, H-20), 4.07 (d, 1H, *J* = 11.7 Hz, H-20), 3.86 (t, 1H, *J* = 2.7 Hz, H-5), 3.06 (d, 1H, *J* = 5.1 Hz, H-3), 2.99 (s, 1H, OH), 2.48-2.25 (m, 3H, 2×H-14, H-9), 2.18-2.04 (4s, 12H, 3×OAc-CH_3, CH_3-18), 1.99-1.87 (m, 1H, H-7), 1.83-1.64 (m, 3H, 2×H-6, H-1), 1.59 (s, 3H, CH_3-16), 1.42 (dd, 1H, *J* = 4.8 Hz, 15.3 Hz, H-9), 1.05 (m, 1H, H-7), 1.00 (t, 9H, TES-$\underline{CH_3}$), 0.98 (s, 3H, CH_3-17), 0.85 (s, 3H, CH_3-19), 0.66 (q, 6H, TES-$\underline{CH_2}$);
   Spectral data of compound **3**: pale yellow film; HR - FABMS (Gly+NaCl)：Found. 679.2932 calcd. 679.2942，$C_{32}H_{52}O_{10}SSi$ +Na; ^{1}H NMR (500 MHz, $CDCl_3$, δppm) 6.02 (dd, 1H, *J* = 12.5 Hz, 5.5 Hz, H-10), 5.29 (dd, 1H, *J* = 2 Hz, 6 Hz, H-2), 5.22 (t, 1H, *J* = 2.5 Hz, H-5), 4.84 (d, 1H, *J* = 12.5 Hz, H-20), 4.55 (dd, 1H, *J* = 6.5 Hz, 9.5Hz, H-13), 4.09 (d, 1H, *J* = 11.7 Hz, H-20), 2.45 (d, 1H, *J* = 5.5 Hz, H-3), 2.42-2.38 (m, 2H, H-14, H-9), 2.24-2.00 (4s+m, 15H, 3×OAc-CH_3, CH_3-18, H-14, H-7, 2×H-6), 1.75 (dd, 1H, *J* = 1 Hz, 7 Hz, H-1), 1.63 (s, 3H, CH_3-16), 1.45 (dd, 1H, *J* = 5.5 Hz, 15 Hz, H-9), 1.29 (m, 1H, H-7), 1.01-0.98 (t+s, 12H, TES-$\underline{CH_3}$, CH_3-17), 0.88 (s, 3H, CH_3-19), 0.68-0.62 (m, 6H, TES-$\underline{CH_2}$);
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