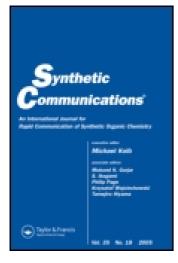
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Novel Route for Preparation of 7-Methylcamptothecin and Its Possible Mechanism

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Abstract: A novel route for preparation of 7-methyl-camptothecin is described. Its possible mechanism is discussed.

Keywords: Mechanism, 7-methyl-camptothecin, novel route, preparation

INTRODUCTION

Camptothecin (CPT),^[1] a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall et al. in 1966, was shown to have strong antitumor activity against colon, mammary, leukemia, and ovarian tumor models. The discovery of its unique mechanism of action, trapping a cleavable complex between topoisomerase I and DNA,^[2] revived the research interest in CPT and its analogs as antitumor agents. A number of CPT analogs have been developed. SAR studies had indicated that a lipophilic group in position 7 such as 7-alkyl-camptothecins are substantially more cytotoxic than CPT.^[3–5] Among 7-alkyl-camptothecins, 7-methyl-camptothecin was the most potent in inhibiting tumor cell growth.^[5]

7-Methyl-camptothecin was previously prepared by treatment of CPT with H_2O_2 , $FeSO_4.7H_2O$, and CH_3CHO in aq. $H_2SO_4^{[5]}$ in moderate yield (<70%). We have found a novel route for preparation of 7-methyl-camptothecin by treatment of CPT with FeSO₄, HCONH₂, and

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 $(CH_3)_3COOH$ under acidic conditions. The present procedure offers several advantages such as much higher yields (96.1%), easy purification of the product (do not need to use column chromatography), and fast reaction time (within 1 h to complete the reaction). This provides an alternative method.

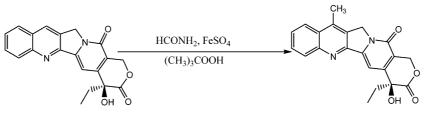
EXPERIMENTAL

Camptothecin (0.1 g, 0.29 mmol) was suspended in a mixture of CF₃COOH (3.5 ml) and H_2SO_4 (1.2 ml). FeSO₄ · 7H₂O (0.21 g, 0.76 mmol) and H₂O (6 ml) were added successively. After cooling to 5° C, HCONH₂ (0.2 ml) was added. To the mixture, 65% (CH₃)₃COOH (0.1 ml, 0.68 mmol) was added dropwise at 2°C. The mixture was stirred for 1 h at 0°C and then poured into ice water. The precipitated material in the solution was collected by suction, washed with water, and dried in vacuo. Yellow powder (0.100 g) was obtained. Yield: 96.1%. IR (KBr) vmax: 3430, 1750, 1653, 1602 cm^{-1} . ¹H NMR (DMSO- d_6) δ : 0.91 (3H, t, J = 7.20 Hz, C18methyl protons), 1.83-1.96 (2H, m, C19-methylene protons), 2.81 (3H, s, C7-CH₃), 5.31 (2H, s, C5-methylene protons), 5.47 (2H, s, C17-methylene protons), 7.35 (1H, s, C14-H), 7.75 (1H, t, J = 7.36 Hz, C10-H), 7.89 (1H, t, J = 7.06 Hz, C11-H), 8.17 (1H, d, J = 8.12 Hz, C9-H), 8.26 (1H, d, J = 8.45 Hz, C12-H). Anal. calcd. for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.01; N, 7.73%. Found: C, 69.40; H, 4.75; N, 7.58%. HRMS (EI) m/z calcd. for C₂₁H₁₈N₂O₄: 362.127; found: 362.129.

DISCUSSION

According to the literature,^[6,7] methylation in the 7 position of CPT in acidic media is presumably a radical mechanism.

The only possible source of methyl radical in Scheme 1 must come from t-butyl hydroperoxide. As Richardson had pointed out,^[8] when t-butyl



7-Methyl-camptothecin

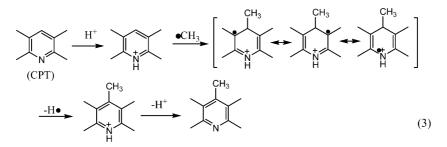
hydroperoxide was used with transition-metal salt, a *t*-butoxy radical was usually produced.

$$Fe^{2+} + (CH_3)_3COOH \longrightarrow Fe(OH)^{2+} + (CH_3)_3CO \bullet$$
(1)

As a common fragmentation, *t*-butoxy radical split into methyl radical and acetone:^[9]

$$(CH_3)_3CO \bullet \longrightarrow \bullet CH_3 + (CH_3)_2CO \tag{2}$$

The methyl radical acted with CPT to afford the methylated species as shown in reaction (3):^[6,7]



It is important to add CF_3COOH to the solvent system because that remarkably improves the solubility of CPT and results in high yield. However, the function of HCONH₂ remained unknown. The fact is that no target product is obtained without the assistance of HCONH₂. We think the function of HCONH₂ may be to stabilize the methyl radical.

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