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CONVERSION OF CAMPTOTHECINS TO MAPPICINE KETONES USING SILICA GEL SUPPORTED SODIUM HYDROGEN SULFATE CATALYST[1]

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Abstract : Silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) catalyst has been utilized for the conversion of camptothecin and 9-methoxycamptothecin to mappicine ketone, an antiviral lead compound and its analogue, 9-methoxymappicine ketone respectively.

The naturally occurring alkaloid camptothecin (**1**)[2,3], originally isolated from *Camptotheca acuminata* Decne (Nyssaceae), has been found[4] to be a promising antitumour agent. The E-ring hydroxylactone of the compound has been established[5] as the most critical structural feature with respect to its antitumour property. The decarboxylated E-ring analogue of camptothecin, known as mappicine ketone (**2**) was found to exhibit no antitumour property but the compound has recently been identified[6,7] as an antiviral lead. The compound has shown significant activity against the herpesviruses (HSV-1 and HSV-2) and human cytomegalovirus (HCMV).

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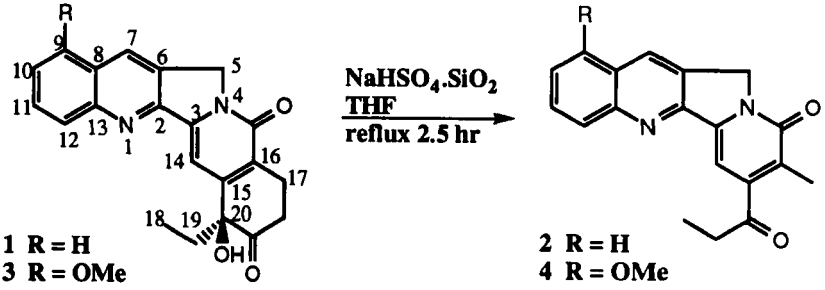
Mappicine ketone (**2**) has been isolated[8] in low yield (0.0001%) from *Nothapodytes foetida* (Wight) sleumer (Icacinaceae) (formerly *Mappia foetida*). Due to such low abundance the isolation of the compound in large quantity from natural source is difficult. Camptothecin (**1**) was earlier converted to mappicine ketone (**2**) by treatment with sodium azide[9] or boron trifluoride etherate[8] as well as by thermolysis[10] or microwave irradiation.[8] In continuation of our work[11,12] on the application of silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) catalyst for the synthesis of bioactive natural products and their intermediates we have recently observed that the catalyst can conveniently be utilized for the conversion of camptothecin (**1**) to mappicine ketone (**2**). The catalyst can easily be prepared from the readily available materials.[13] Previously it was applied for dehydration and acetylation of alcohols[14-16], one-pot conversion of aldehydes to nitriles[12] and selective esterification of aliphatic carboxylic acids.[17] During our present study camptothecin (**1**) was refluxed in dry THF in the presence of $NaHSO_4.SiO_2$ catalyst for 2.5 hr to afford mappicine ketone (**2**) in 68% yield. 9-Methoxycamptothecin (**3**)[8] another naturally occurring alkaloid, when treated with the catalyst under similar conditions, produced 9-methoxymappicine ketone (**4**) (yield 66%).



In summary, we have developed a simple and useful method by using $NaHSO_4.SiO_2$ catalyst for the conversion of camptothecin and 9-methoxycamptothecin to mappicine ketone, an antiviral lead compound and its

analogue, 9-methoxymappicine ketone respectively. The use of inexpensive and non-hazardous catalyst, operational simplicity and the high yields of the products can make the present procedure an attractive alternative to the currently available conventional methods. A new utilization of the catalyst ($NaHSO_4.SiO_2$) has also been discovered.

Experimental:

Conversion of camptothecin (1) to mappicine ketone (2):

To a suspension of camptothecin (**1**) (100 mg) in dry THF (50 ml) $NaHSO_4.SiO_2$ (500 mg) was added. The mixture was refluxed for 2.5 hr and then filtered. The filtrate was concentrated. The solid mass was purified by column chromatography over silica gel using EtOAc as eluent. The product was isolated and further purified by crystallization from $CHCl_3$ to afford mappicine ketone (59 mg, 68%). Unreacted camptothecin (24 mg) was recovered.

Mappicine ketone (2):

M.p. 213-214°C ($CHCl_3$) [lit.[18] 214-215°C]; IR : 1694, 1653, 1596 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.37 (1H, s, H-7), 8.18 (1H, dd, J=8.6, 1.4 Hz, H-12), 7.91 (1H, dd, J=8.6, 1.4 Hz, H-9), 7.82 (1H, dd, J=8.6, 1.4 Hz, H-11), 7.63 (1H, dt, J=8.6, 1.4 Hz, H-10), 7.22 (1H, s, H-14), 5.29 (2H, s, H_2-5), 2.89 (2H, q, J=7.0 Hz, H_2-19), 2.30 (2H, s, M_2-17), 1.28 (3H, t, J=7.0 Hz, Me-18); MS : m/z (%) 304 ($M^{+\cdot}$ 22), 289 (7), 248 (18), 219 (20), 191 (2), 125 (8). Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.87; H, 5.33; N, 9.28. The structure of the product **2** was confirmed by direct comparison with an authentic sample of mappicine ketone.[18]

Conversion of 9-methoxycamptothecin (3) to 9-methoxymappicine ketone (4):

9-Methoxycamptothecin (**3**) (100 mg) was treated with $NaHSO_4.SiO_2$ (500

mg) catalyst under the similar conditions as mentioned above to produce 9-methoxymappicine ketone (**4**) (58 mg, 66%). Unreacted 9-methoxycamptothecin (21 mg) was recovered.

9-Methoxymappicine ketone (4):

M.p. 237-238°C ($CHCl_3$), [lit.[18] 236-237°C ($CHCl_3$)]; IR : 1691, 1652, 1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.76 (1H, s, H-7), 7.80-7.62 (2H, m, H-11 and H-12), 7.21 (1H, s, H-14), 6.92 (1H, dd, J=6.0, 2.5 Hz, H-10), 5.24 (2H, s, H_2-5), 4.06 (3H, s, -OMe), 2.90 (2H, q, J=7.0 Hz, H_2-19), 2.28 (3H, s, Me-17), 1.27 (3H, t, J=7.0 Hz, Me-18); MS : m/z (%) 334 (M^+, 100), 319 (42), 279 (44), 234 (12), 207 (10). Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.75; H, 5.41; N, 8.41. The structure of the product **4** was confirmed by direct comparison with an authentic sample of 9-methoxymappicine ketone.[18]

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