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Vinyl Isocyanates in Alkaloid Synthesis. Camptothecin Model Studies.

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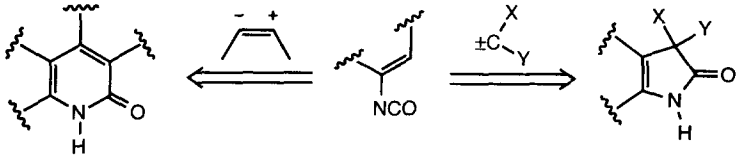
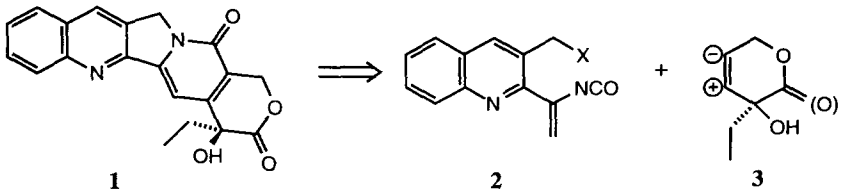
Abstract: Model studies directed toward camptothecin employing a vinyl isocyanate-enamine cyclocondensation as the key synthetic step are reported. © 1997 Elsevier Science Ltd.

Vinyl isocyanates have been found to serve as versatile and reactive 2-azadiene equivalents in a number of contexts.[1,2] These readily available functions can be viewed as 1,4-dipole equivalents and can deliver five-membered nitrogen heterocycles when reacted with 1,1-dipoles, such as alkyl isocyanides or nucleophilic carbenes.[1] In addition, rapid access to substitutionally elaborate 2-pyridones can be achieved by treating vinyl isocyanates with appropriate 1,2-dipolar partners, including enamines, ester enolates and benzyne.[2]

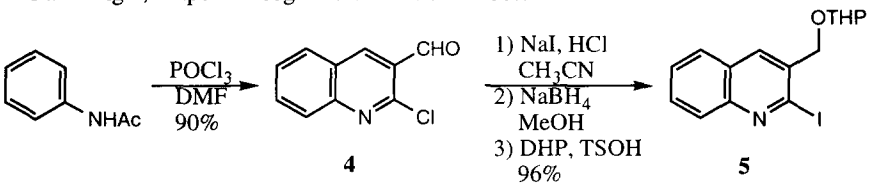


The reemergence of camptothecin (**1**)[3] as a selective inhibitor of mammalian topoisomerase I has prompted a flurry of recent synthetic activity that has culminated in several impressive total syntheses.[4] Furthermore, analogs of camptothecin possessing improved water solubility are now at various stages of clinical evaluation.[5] Vinyl isocyanate-enamine cyclocondensation[2c] could offer a novel entry into the pyridone D-ring substructure of camptothecin, and model studies in this area are reported herein.



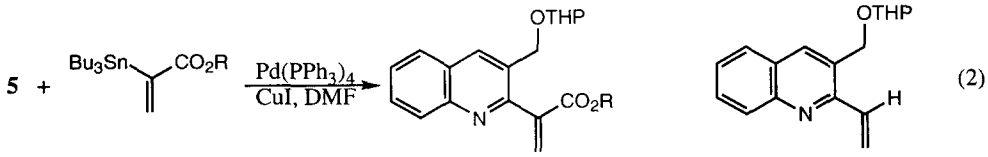
1 **2** **3**

The basic synthesis strategy employed in these studies features the cyclization between a quinoline vinyl isocyanate **2** and a 1,2-dipolar version of the E-ring building block **3** to construct the alkaloid in a one-step, double-ring forming process. To establish the viability of this cyclization protocol, 1-pyrrolidino-1-cyclohexene was used as a E-ring 1,2-dipole surrogate in these model studies.



(1)

The requisite quinoline moiety was prepared in excellent overall yield as depicted in equation (1). Treatment of acetanilide with $POCl_3$ in dimethyl formamide afforded the known compound **4**[6], and routine conversion into the 2-iodoquinoline **5**[7,8] followed in virtually quantitative yield. Next, Pd(0)-mediated cross-coupling of **5** and 2-tributylstannyl acrylic acid (**6**),[9] prepared in 95% yield by Pd(0)-promoted hydrostannylation of propiolic acid, provided compound **7a**[8] in 61% yield.[10] It is noteworthy that coupling with the corresponding acrylate methyl ester afforded **7b** in 90% yield, but subsequent efforts to saponify this material to the required carboxylic acid afforded only the decarboxylated vinyl quinoline **8**.



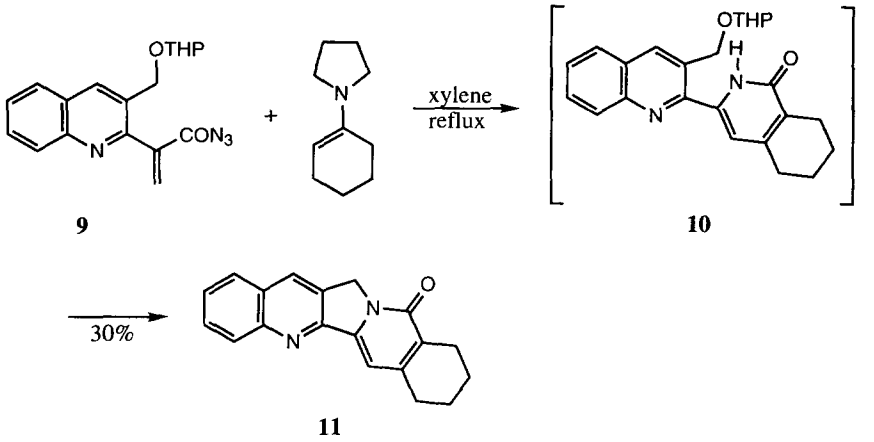
(2)

6

7a, R = H (61%)
7b, R = Me (90%)

8

With the substituted acrylic acid **7a** in hand attention turned to the key ring-forming step. Exposure of **7a** to diphenyl phosphorazidate (DPPA) afforded the requisite acyl azide **9**[8] in an unoptimized 31% isolated yield. At this juncture the plan called for treating azide **9** with 1-pyrrolidino-1-cyclohexene at elevated temperatures in an attempt to effect Curtius rearrangement to the isocyanate followed immediately by cyclocondensation with the enamine to give the pyridone intermediate **10**. Further cyclization of this species to provide the C-ring of the camptothecin-like target would complete the sequence without isolation of any intermediates. In the event, heating **9** with excess enamine in xylene at reflux afforded the desired pentacyclic product **11**[8] in 30% isolated yield from the acyl azide in only one operation!



Although the yield of this overall conversion is modest, fully three events have been effected without intervening isolation or purification. Consequently, this approach may permit rapid assembly of the natural product itself. Work is currently ongoing to extend this synthetic approach to the synthesis of camptothecin itself.

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