Tetrahedron Letters,Vol.24,No.30,pp 3065-3066,1983 0040-4039/83 $3.00 + .00
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A NOVEL SYNTHESIS OF THE CYCLIC CARBINOLAMIDE MOIETY OF THE MAYTANSINOIDS

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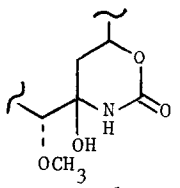
Summary: The α-diketo urethane 3 cyclizes to form the cyclic carbinolamide 4 using TMS triflate and 2,6-di-t-butylpyridine. The siloxy group of 4 is readily exchanged in methanol or water to form 6 or 7. Remarkably, 3 does not cyclize spontaneously or on standard acid catalysis.

The cyclic carbinolamide moiety 1 has been proposed as one of the reactive sites responsible for the cytotoxic, antimitotic and antileukemic properties of the maytansinoids, presumably via an alkylation mechanism.[1] With this in mind, a number of syntheses have been devised leading to model carbinolamides[2-6] or to the maytansinoids themselves.[7,8]

We had previously described a synthesis of the methyl ether of the α-keto N-methyl carbinolamide 2,[6] using an approach which, unfortunately, proved inapplicable to the synthesis of the nonmethylated species. We now wish to report a novel and efficient synthesis of this latter type which makes use as starting materials of the α-diketones described in the preceding communication.[9] The diketo alcohol 3 ($CONH_2$=H) was converted into the urethane 3 with anhydrous cyanic acid in chloroform by a modification of the published procedure.[10] In contrast to the ease with which α-keto aldehydes condense with urethanes to form carbinolamides[6,11] the diketo



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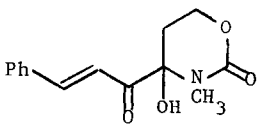

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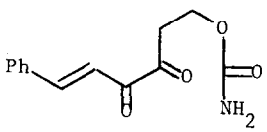

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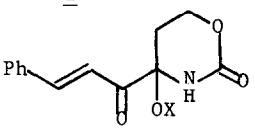
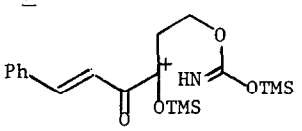


4 X = TMS
6 X = CH_3
7 X = H



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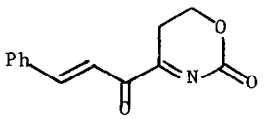

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urethane 3 resisted cyclization to form 7 using conventional acid catalysts, e.g., Nafion-H®,[12] TFA, or TMSCl/DMAP. Only the powerful silylating agent-Lewis acid TMS triflate[13] in the presence of the non-nucleophilic base 2,6-di-t-butylpyridine was capable of effecting ring closure to form the TMS-ether 4 in excellent yield. Two equivalents of the reagent were required, which suggest the intermediacy of the bis-silyl ether carbonium ion 5. Solvolysis of

4 in methanol or THF/water furnished 6 and 7, respectively, in excellent yield. Moreover, the latter two compounds were interconvertible in the presence of TFA at rates very similar to those reported for the maytansinoids.[14] This finding suggests the intermediacy of the reactive keto acylimine 8 in the solvolysis reaction[15] proposed by Lown et al.[3] for structures of type 1. This view is supported by the finding that 2 (NCH_3!) is stable in the presence of TFA.[16] The α-ketocarbinolamides of structure 7 would therefore be expected to possess alkylating properties similar to those of structure 1.[3]

Diketourethane 3. A solution of HNCO was prepared by stirring a suspension of NaNCO (455 mg, 7.0 mmole) in $CHCl_3$ at 0° with TFA (385 µl, 5.0 mmole) for 15 min and filtering the mixture through glass wool into the diketoalcohol 3 (H=$CONH_2$, 250 mg, 1.23 mmole) at 0°. After 13 hrs (60% conversion) at 25° additional HNCO (550 mg NaNCO, 470 µl TFA) was added to complete the reaction in 12 hrs. Workup with dilute HCl gave 298 mg (82%) of urethane 3 (85% pure by NMR). 500 MHz NMR ($CDCl_3$, δ): 3.19 (t, J=6, 2H); 4.44 (t, J=6, 2H); 4.62 (broad, ∿ 2H); 7.32-7.64 (m, 6H); 7.82 (d, J=16, 1H). IR ($CDCl_3$, cm^{-1}): 3550, 3440, 1730, 1680, 1610. m/e: 131.0502 (100%, $C_6H_5CH=CHCO$), 116.0348 (2.23%, $NH_2CO_2C_2H_4CO$).

Cyclization of 3. To the diketocarbamate 3 (200 mg, 85% pure, 0.69 mmole) and 2,6-di-t-butylpyridine (315 µl, 1.4 mmole) in $CDCl_3$ (7 ml) at -50° was slowly added TMS triflate (135 µl, 0.67 mmole). After 1 hr, slowly warmed to 0°, NMR indicated 40% completion. Addition of base (394 µl) and TMS triflate (204 µl) at -50° was repeated. CH_3OH (7 ml) was added at -20° and the mixture allowed to warm slowly to 25°. After 13 hrs workup with CH_2Cl_2 and pH 7 buffer and flash chromatography gave 214 mg of 3 (95% pure by NMR). ^1H NMR: 0.12 (s, 9H); 1.87 (m, J=16, 11, 5, 1H); 2.13 (broad d, J=16, < 7, 1H); 4.39 (broad d, J=13 < 7, 1H); 4.63 (m, J=13, 11, 3, 1H); 7.06 (d, J=17, 1H); 7.34-7.59 (m, 5H); 7.85 (d, J=17, 1H). IR: 3400, 1720, 1610 cm^{-1}. m/e: 319.1261 (M^+, .91%), 188.0754 (M-$C_6H_5CH=CHCO$, 37%), 131.0493 (100%).

Support by NIH (AM 21846, CA 09183 and AM 11499) is gratefully acknowledged.

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(Received in USA 21 April 1983)