The Chemistry of Vicinal Tricarbonyls. New Routes to Indolizidines

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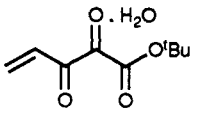
Summary: The vinyl tricarbonyl system **1** reacts as a trielectrophile with reagents having multiple donor capability to form functionalized indolizidines.

The central carbonyl group in a vicinal tricarbonyl system has attracted attention as a highly electrophilic site. We have recently demonstrated the synthetic utility of this reactive unit in the formation of fused ring β-lactams[1] and natural products in the vincamine,[2] isoquinoline,[3] and prodigiosin[4] families. We now report a novel method for preparing indolizidines[5] using the vinyl tricarbonyl reagent **1**.[6] Methods for the formation of the indolizidine ring system are of timely concern in connection with current interest in the biological properties of alkaloids such as swainsonine,[7] castanospermine,[8] and slaframine.[9]



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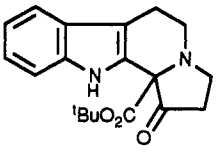

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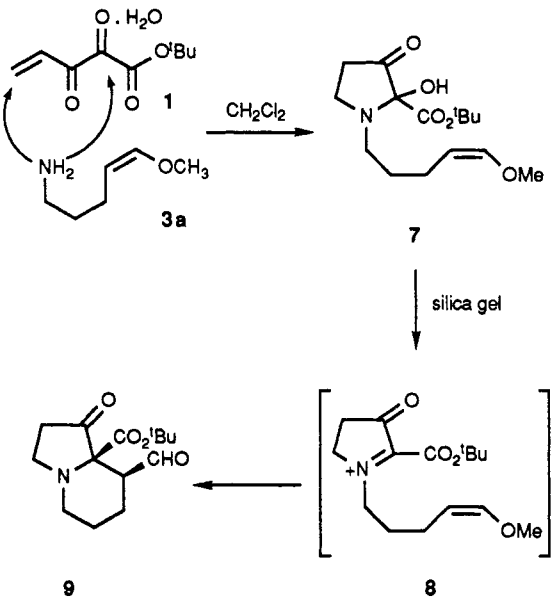
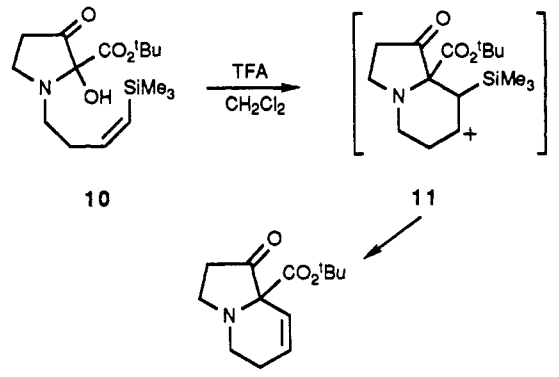
Because of the concentration of electron-deficient groupings in a small carbon skeleton, compound **1** is a potent trielectrophile as revealed in its facile incorporation of tryptamine into the tetracyclic addition product **2**.[6] We have now found that with other primary amines possessing auxiliary donor sites, the same type of reaction leads to substituted indolizidines. The multinucleophilic reagents shown in Figure 1[10] initially take part in a 2-fold addition of the amine to the α,β-unsaturated ketone and the central carbonyl group in **1**, generating a hydroxypyrrolidinone carboxylate. Under acid conditions this intermediate forms an iminium salt which acts as an acceptor for a third-stage nucleophilic attack, aided by the electron-donor capability of either an enol ether, a vinylsilane, a propargylsilane, or a pyrrole.

The cis enol ether **3a**[11] reacts with **1** to form hydroxypyrrolidinone **7**. Cyclization to the indolizidine **9**[13,14] (Scheme I) occurs readily, apparently through the salt **8**,

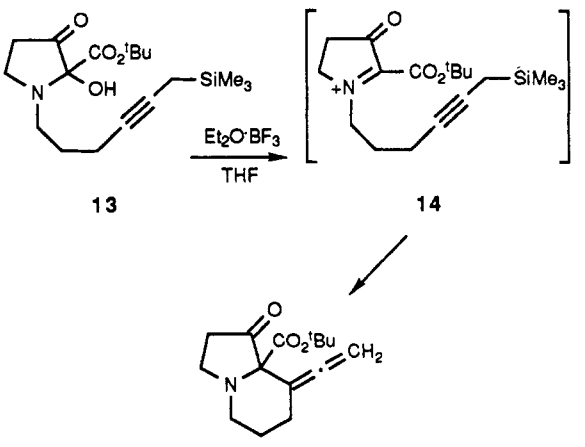
Scheme I



Scheme II



Scheme III



(1) (a) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743. (b) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747. (c) Wasserman, H. H.; Han, W. T. *J. Am. Chem. Soc.* **1985**, *107*, 1444.
(2) Wasserman, H. H.; Kuo, G.-H. *Tetrahedron Lett.* **1989**, *30*, 873.
(3) Wasserman, H. H.; Amici, R.; Frechette, R.; van Duzer, J. *Tetrahedron Lett.* **1989**, *30*, 869.
(4) Wasserman, H. H.; Lombardo, J. L. *Tetrahedron Lett* **1989**, *30*, 1725.
(5) For recent reviews on methods of preparing indolizidines, see: Howard, A. S.; Michael, J. P. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1986; Vol. 28, p 183. Rajeswari, S.; Chandrasekharan, S.; Govindachari, T. R. *Heterocycles* **1987**, *25*, 659.
(6) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.
(7) Bennett, R. B. III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580 and references cited therein.
(8) Reymond, J.-L.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 705 and references cited therein.
(9) Harris, T. M.; Schneider, M. J. *J. Org. Chem.* **1984**, *49*, 3681 and references cited therein.
(10) For other examples of π-donor groups used in intramolecular cyclizations, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(11) 5-Methoxy-4-penten-1-amine was prepared from 5-methoxy-4-penten-1-ol by mesylation (94%), phthalimide displacement (90%), and methanolic hydrazinolysis (97%). The alcohol was made by a Wittig reaction of (methoxymethyl)triphenylphosphorane with 2-hydroxyfuran (91%, trans/cis = 2/1) using conditions described by Clive.[12] The trans and cis isomers may be readily separated at the mesylate stage.

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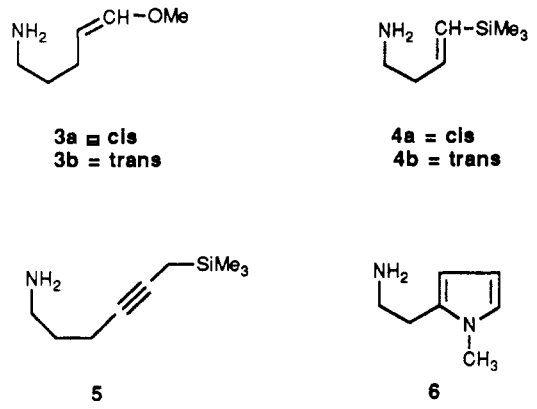
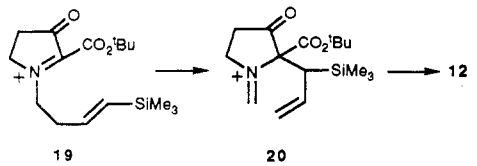


Figure 1.

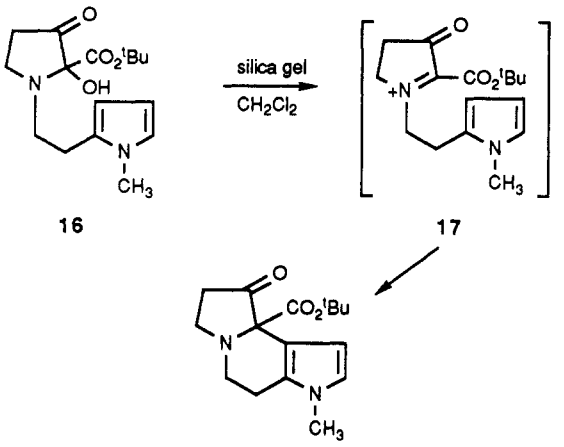
upon addition of silica gel (45% overall). The trans enol ether **3b** yields a mixture of the cyclized product (20%) and 3-hydroxypyrrole-2-carboxylate (16%)[15] under the same conditions.[16]

The vinylsilane derivative **4a**[17] takes part in a related acid-promoted cyclization most probably through the stabilized carbonium ion **11** (Scheme II). Here again, it is the cis derivative which leads to an indolizidine derivative (42% overall) while the trans analogue **4b** gives only a small amount of hydroxypyrrole rather than **12**. These results are in accord with the recent findings of Overman, wherein cis vinylsilanes add preferentially to iminium ions presumably by enhanced hyperconjugative stabilization of the intermediate carbonium ion.[18-20]

(12) Clive, D. L. J.; Ångoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339.
(13) All new compounds were characterized by ^{1}H NMR, IR, MS, and high-resolution MS.
(14) In practice, these cyclizations were carried out in one pot by treating the hydroxypyrrolidinone directly with silica gel or Lewis acids.
(15) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721.
(16) In the presence of a Lewis acid ($Et_2O{\cdot}BF_3$, $POCl_3$) or PPTS, **3b** undergoes exclusive conversion to **9** (35%).
(17) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097.
(18) For a recent review of vinyl silane and alkynylsilane-terminated cyclizations, see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
(19) A related iminium ion initiated, vinylsilane-terminated cyclization reaction to generate indolizidines has recently been reported. Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.
(20) A referee points out that failure to observe formation of **12** from the reaction of **1** with the trans isomer **4b** may rule out an alternative process shown in the transformation of **19** to **12** through **20**, for which there is precedent.[18]



Scheme IV



The propargylsilane derivative **5**[21,22] undergoes rapid conversion to the allene **15** (64% overall) as illustrated in Scheme III. As observed in related propargyl systems[17,21] iminium ion formation and cyclization take place in preference to the competing protodesilylation.

The efficiency of these intramolecular cyclizations appears to be dependent upon the nucleophilic strength of the third-stage nucleophile. Accordingly, when an electron-rich *N*-methylpyrrole is appropriately appended to the primary amine as in **6**, a facile cyclization takes place. The tricyclic system **18** can be obtained in 90% overall yield through this three-step sequence when the intermediate carbinolamine **16** is treated with a mildly acidic reagent such as silica gel (Scheme IV). This cyclization, like the previous examples, offers the advantage of placing an oxygen functionality at the C-1 position of the indolizidine ring. The fused *N*-methylpyrrole ring thus created, provides a reactive site for further elaboration.

In summary, our method provides a novel, generally applicable route to the indolizidine system. Current work will investigate the use of these precursors in the synthesis of derivatives of biological interest.

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Supplementary Material Available: Spectroscopic data for all new compounds (3 pages). Ordering information is given on any current masthead page.

(21) Hiemstra, H.; Sno, M.; Vijn, R.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.
(22) 6-(Trimethylsilyl)-4-hexyn-1-ol[21] was converted to the corresponding azide (75%) by treatment with diphenyl phosphorazidate in the presence of diisopropyl azodicarboxylate and triphenylphosphine: Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467. Reduction of the azide with $LiAlH_4$ in Et_2O gave the substituted amine **5** (91%).