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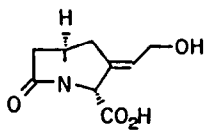
FREE-RADICAL ANNELATION IN THE SYNTHESIS OF BICYCLIC β-LACTAMS. 6.[1] SYNTHESIS OF tert-BUTYL 2-BENZYLIDENE-1-CARBAPENAM-3-CARBOXYLATE

Mario D. Bachi*, Alain De Mesmaeker and Nadine Stevenart-De Mesmaeker
Department of Organic Chemistry,
The Weizmann Institute of Science, Rehovot, Israel

Summary: *tert*-Butyl 2-benzylidene-1-carbapenam-3-carboxylate was obtained through the homolytic cyclization of a suitably substituted nonfused β-lactam

The hypothetetical 1-carbaclavulanic acid **1** is of interest, due to its structural similarity to the β-lactamase inhibitor clavulanic acid **2**[2] and to carbapenem antibiotics related to thienamycin and olivanic acid represented by the general structure **3**.[3] Although the parent compound **1** has not been reported in the literature, there are references to the 2-alkylidene-1-carbapenam-3-carboxylate **4**$_{a-d}$.[4-7] These compounds were obtained as secondary products in studies aiming at the synthesis of carbapenems of type **3** bearing an endocyclic rather than an exocyclic double bond at position-2. Recently, a few carbapenams bearing an exocyclic methylene group at position-2, but lacking a carboxylate function were synthesized.[8-9]



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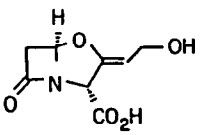

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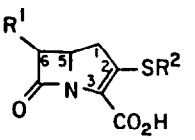

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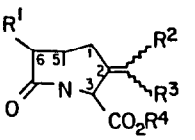
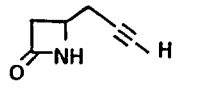


4

a, R^1 = H; R^2 = Ph; R^3 = CO_2Me; R^4 = CH_2Ph
b, R^1 = Et; R^2 = CN; R^3 = CO_2Me; R^4 = CH_2-C_6H_4-NO_2-p
c, R^1 = Me; R^2 = R^3 = H; R^4 = CH_2-C_6H_4-NO_2-p
d, R^1 = Me(F)CH; R^2 = H; R^3 = CN; R^4 = K



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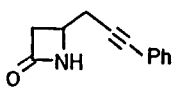

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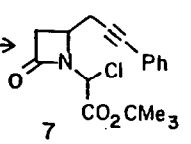

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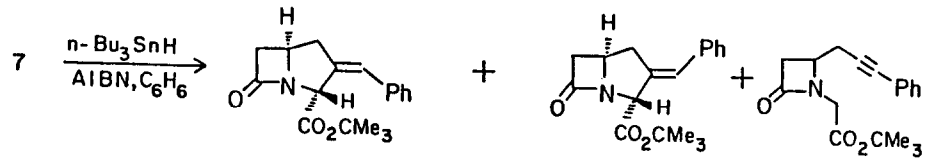

8 9 10

We now describe the synthesis of *tert*-butyl 2-benzylidene-1-carbapenam-3-carboxylates **8** and **9** by a method expected to be of general applicability for the preparation of carbaclavulanic acid analogs. The key reaction in this synthesis involves the free-radical cyclization of the acetylenic chloro lactam **7**.[10] This compound

was readily obtained from the N-unsubstituted β-lactam **6** and *tert*-butyl glyoxalate by a conventional method.[11] 4-Phenylpropargylazetidin-2-one **6** is best prepared (81%) by reacting 4-propargylazetidin-2-one **5**[12] with phenyl iodide in triethylamine under CuI, $Pd(Ph_3P)_4$ catalysis.[13] The annelation of the acetylenic chloro lactam **7** was accompanied by the formation of some nonfused reduced β-lactam **10** in variable amounts, depending on reaction conditions. In a typical experiment, individual benzene solution of tri-n-butylstannane (1.1 equivalent) and azobisisobutyronitrile (0.05 equivalent) were simultaneously added, during 3 h, to a boiling solution of the chloro lactam **7** in benzene (0.003 M). ^{1}H NMR analysis of the product, obtained after removal of the tin compounds, indicated an almost quantitative conversion into a mixture of the β-lactams **8**, **9** and **10** in a ratio of 5.1:2.6:1. Flash chromatography separation (silica gel, CH_2Cl_2-Et_2O) afforded *tert*-butyl 2-benzylidene-1-carbapenam-3-carboxylates **8** and **9** (66%) and the nonfused β-lactam **10** (10%).[14] In this synthesis, the highly strained and chemically reactive fused bicyclic system is completed simultaneously with the formation of the exocyclic double bond and does not need any additional manipulation with functional groups. The relative configuration of the carboxylate group versus the bridgehead hydrogen atom in the carbapenams **8** and **9** is the same as that observed in clavulanic acid.

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References and Notes

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14. a) All new compounds gave IR, ^{1}H NMR, and high resolution MS consistent with the assigned structures. b) Selected spectral data: **8**: υ (film) 1773, 1734 cm^{-1}. δ ($CDCl_3$) 1.33 (s, CMe_3), 2.64 (dddd, J=17.0, 4.7, 2.0, <1.0Hz, 1β-CH), 2.77 (ddd, J=16.0, 2.4, 1.0Hz, 6β-CH), 3.22 (dddd, J=17.0, 8.0, 1.9, 1.9Hz, 1α-CH), 3.42 (dd, J=16.0, 5.2Hz, 6α-CH), 4.07 (m, 5α-CH), 5.22 (m, 3β-CH), 6.60 (m, C=CH). **9**: υ (film) 1773, 1734 cm^{-1}. δ ($CDCl_3$) 1.50 (s, CMe_3), 2.63 (dddd, J=17.2, 6.0, 2.6, 1.6Hz 1β-CH), 2.77 (ddd, J=15.8, 1.9, 1.0Hz, 6β-CH), 3.22 (dddd, J=17.2, 7.2, 2.0, 1.9Hz, 1α-CH), 3.45 (dd, J=15.8, 4.9Hz, 6α-CH), 4.14 (m, 5α-CH), 4.98 (m, 3β-CH), 6.68 (m, C=CH).

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