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REACTION OF N-STYRYL-1,2-DIHYDROPYRIDINE WITH DIMETHYL ACETYLENEDICARBOXYLATE. PREPARATION OF AN N-VINYLDIHYDROAZOCINE.

Patrick S. Mariano,* Morey E. Osborn and Emil Krochmal, Jr.
Department of Chemistry, Texas A&M University, College
Station, Texas 77843.

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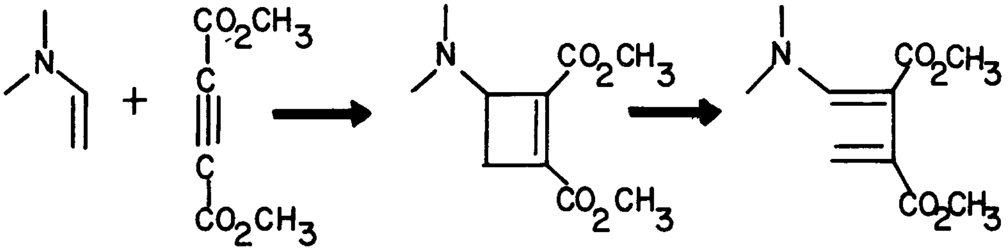
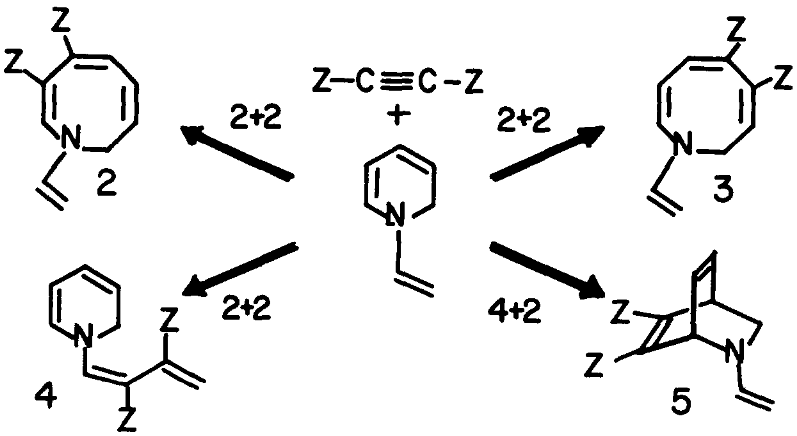
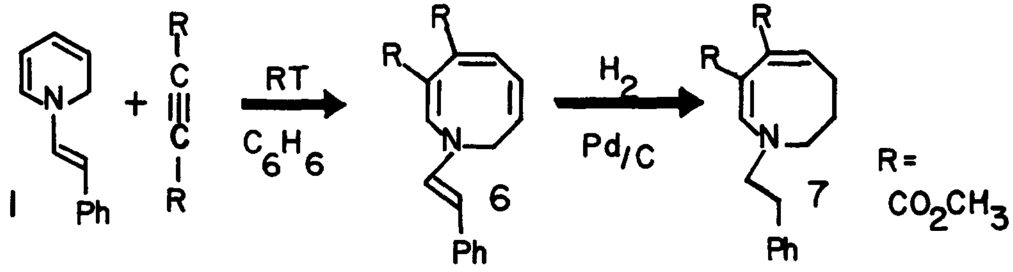
Several investigations of reactions of enamines with acetylenedicarboxylates, leading to linear dienamines via cyclobutene containing intermediates, have been reported. Examples are known in which the enamine moiety is acyclic,[1] part of a vicinyl endiamine group,[2] and in which the ene-portion is contained within a medium-ring system.[3] As part of an effort directed at new synthetic applications of N-vinyl-1,2-dihydropyridines and N-vinyl-2-pyridones,[4] we have investigated the reaction of dimethyl acetylene dicarboxylate with N-trans-β-styryl-1,2-dihydropyridine (1). This ambident trienamine contains several reaction sites for both 2+2[5] and 4+2[6] cycloaddition by the acetylene derivative. As a result, reactions of N-vinyl-1,2-dihydropyridines with acetylene derivatives have the potential of yielding N-vinyldihydroazocines, such as 2 and 3, N-butadienyl-1,2-dihydropyridines, 4, and or the interesting N-vinyl-2-azabicyclo[2.2.2]octa-4,7-dienes, 5. In view of this, the observation of a regioselective and efficient reaction leading to the N-styryl-dihydroazocine 6 from 1 and dimethyl acetylenedicarboxylate is interesting, since it offers a potentially general method for preparation of compounds in this series, containing the dihydroazocine ring system and the exocyclic enamine functionality possibly useful for further structural



elaboration.



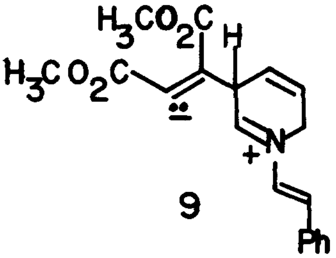
Preparation of N-styryl-1,2-dihydropyridine (1), used in this study, was by a modification[7] of the method of Berg and co-workers.[8] We have found that exceptionally pure[9] 1 can be obtained by sublimation (95°C, 0.01 mm) of the crude material obtained from the sodium borohydride reduction of N-styrylpyridinium iodide in the presence of base. The reaction of 1 (0.83 g, 4.55 mmol) with dimethyl acetylenedicarboxylate (0.97 g, 6.82 mmol) was conducted at room temperature in benzene (25 ml) for 19 hr under an argon atmosphere. Silica gel chromatography (45% ether-hexane elution) of the crude reaction mixture after solvent removal gave 1.02 g (69%) of the partially crystalline 6, which resisted further purification attempts. The proton nmr spectrum (CCl_4) of this compound contains resonances at the proper chemical shifts and with the correct multiplicities for the assigned structure. Characteristic among these are the <u>trans</u>-styryl AB quartet (δ 5.89 and 6.85, J=14Hz), C-1 proton singlet (δ 7.72), two methyl singlets, and $ABCX_2$ pattern for the remaining ring protons. Similarly, the C-13 nmr spectrum ($CDCl_3$), with distinguishing resonances at 44.2 (t, C-8), 51.7 and 52.3 (q, CH_3's), 100.6 (s, C-3) and 145.3 ppm[10] (d, C-2) are in accord with the dihydroazocine skeleton. Additional spectral data are as follows: uv (EtOH)



λ_{max} 325 (22,000), 263 (9,000), and 227 nm (14,000); *ir* (CCl_4) 1721 (C=O), 1593 (C=C), 1140 cm^{-1} (C-N); *mass spec.* (m/e), 325 (P, 100%), 266($P-CO_2CH_3$, 93%), and 103 (PhCH=CH, 52%); and *high resol. mass spec.*, found, 325.1304, and calcd. for $C_{19}H_{19}NO_4$, 325.1309.

Catalytic hydrogenation of **6** (151 mg in 50 ml abs. MeOH, Pd/C, 55psi) gave N-2-phenylethyl-1,2,3,4-tetrahydroazocine (**7**) (37%), whose characterization was accomplished by spectral methods and molecular formula.[11] In addition to the C-13 nmr spectrum, which displayed the correct number of saturated and unsaturated carbons with correct multiplicities, the H-nmr spectrum contained vinyl resonances at δ 7.33 (s, 1H) and 6.13 (t, J=8Hz, 1H), assigned to the ring protons at C-2 and C-5, respectively.

The reaction of N-*trans*-β-styryl-1,2-dihydropyridine (**1**) with acetylene dicarboxylate appears to parallel those observed[5] for N-substituted-1,2-dihydropyridines not having the extra exocyclic enamine moiety. The regioselectivity of the initial 2+2 cycloaddition, yielding an intermediate 2-azabicyclo[4.2.0]octadiene, **8**, appears, therefore, to be governed by electron density within the delocalized, cross-conjugated trienamine chromophore, which is expected to be greater at the C-5 carbon than at either C-3 or C-1' of the styryl moiety within **1**. Thus, a nonconcerted reaction leading to **8**, through the zwitterion **9**, appears reasonable.



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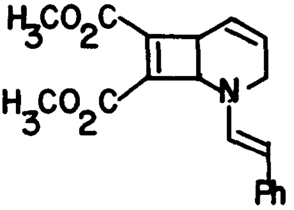

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In summary, the observed reaction appears useful in sequences designed to prepare N-functionalized-1,2-dihydroazocines. Further studies are underway in our laboratory to explore the synthetic potential of this process as well as other aspects of N-vinyl-1,2-dihydropyridine chemistry.

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)) The sublimed **1** is a yellow crystalline solid which is unstable in air. The crude material, however, survives storage *in vacuo* for extended periods. The pure material (mp 103-104, lit[8] mp 103-107°) is used *immediately* after sublimation.

)) Carbon chemical shifts are given relative to tetramethylsilane as the internal standard.

) The remaining spectral data for **7** are as follows: *H-nmr* (CCl_4) δ 1.4-1.2 (m, 2H, H-7), 2.33 (m, 2H, H-6), 3.47-2.67 (A_2B_2m, 4H, H-1' and H-2'), 3.50 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.90 (t of m, 2H, J=15Hz, H-8), 6.13 (t, 1H, J=8Hz, H-5), 7.17 (s, 5H, arom) and 7.33 (s, 1H, H-2); *ir* (CCl_4) 1720 and 1688 (C=O), 1585 (C=CCO), 1260 (C-O), 1175 (C-N) and 693 cm^{-1} (arom); *mass spec*. (m/e) 329 (P,28%), 298 ($P-OCH_3$, 15%), 270 ($P-CO_2CH_3$, 11%), 238 ($P-PhCH_2$, 100%) and 91 ($PhCH_2$, 28%); *high resol. mass spec*., found 329.1619 and calcd. for $C_{19}H_{23}NO_4$, 329.1627.