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SYNTHESIS OF 1-AZASPIRO[5.5]UNDEC-7-EN-2-ONE

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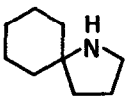
The 1-azaspiro[4.5]decane (1) and 1-azaspiro[5.5]undecane (2) ring systems are important structural features of a variety of natural alkaloids [1] In addition, synthetic



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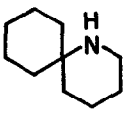

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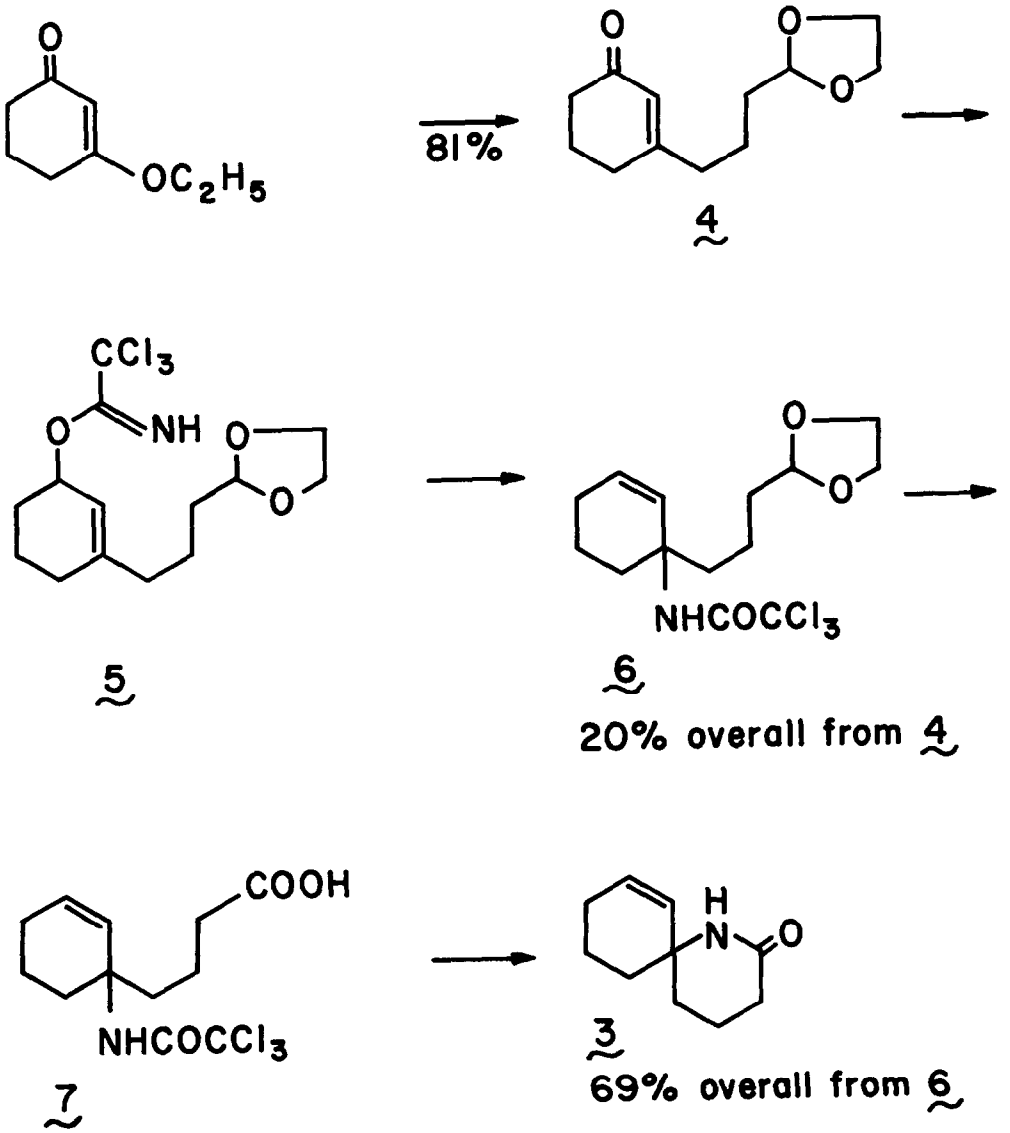
compounds with these ring systems have been reported to display a broad spectrum of pharmacological activities [2] Although a fairly large number of synthetic routes exist for the synthesis of 1-azaspiranes functionalized in the azacyclic ring, [3] synthetic approaches which allow for versatile incorporation of functionality in the carbocyclic ring are conspicuously absent In this letter, we report a potentially general route to such systems which regiospecifically incorporates unsaturation in the carbocyclic ring

In particular we wish to describe a short route to the unsaturated spirolactam 3, which is based on our recently reported[4] method for the 1,3-transposition of oxygen and nitrogen functionalities Spirolactam 3 contains synthetic handles for further elaboration of functionality at carbons 2, 7, and 8, and thus is a potential precursor to the ring system of the anticholinergic, histrionicotoxin alkaloids [1]

Grignard addition of readily available[5] 1-ethylenedioxy-4-chlorobutane to 3-ethoxy-2-cyclohexenone afforded, after hydrolysis at pH 1 5, enone 4[6] in 81% yield, b.p 135-140 (.01 torr). Reduction of 4 with $LiAlH_4$ (2 equiv) in THF at -78° yielded quantitatively the corresponding alcohol Treatment of this alcohol with sodium hydride (15 equiv) in ether, followed by addition at 0° of the resulting alcohol-alkoxide solution to an ethereal solution of trichloro-acetonitrile (1 1 equiv) afforded the allylic trichloroacetimidate 5,[6] which was not purified, but directly thermally rearranged by heating at 69° in hexane for 4-5 days After separation of the insoluble by-product, trichloroacetamide (45-55% yield), the rearranged amide 6 crystallized directly from the concentrated hexane solution; 20% overall yield from 4; mp 90 5-91 5°; ir (KBr) 3200, 1701, and 1511 cm^{-1}, pmr (CCl_4) τ 3 72 (1H, broad s, NH) and 4 11 (2H, broad s, = CH) No trace of the allylic isomer of 6 could be found upon careful examination of the crude reaction mixture by pmr The major products formed, in addition to 6, are a mixture of dienes resulting from the loss of trichloroacetamide from 5 Oxalic acid catalyzed hydrolysis of 6 in acetone-water (4 1) followed directly by oxidation with AgO[7] afforded acid 7[6] (mp 110-111 5°) in essentially quantitative yield. Treatment of 7 at 25° with 3M NaOH for 2 hr, followed by removal of the water and esterification (H_2SO_4 in methanol) gave the corresponding amino ester which spontaneously cyclized when basified to afford spirolactam 3;[6,8] 69% overall yield from 6; mp 117-118°; ir (KBr) 3190, 3050, 1663 cm^{-1}; pmr (CCl_4) τ 2 41 (1H, broad s, NH), 4 13-4 67 (2H, m, = CH)

The yield of amide 6 from the thermal rearrangement of imidate 5 is disappointingly low, and in fact is the lowest we have observed for a secondary allylic trichloroacetimidate [4] However, the high yields of the other steps and the fact that only two intermediates, 4 and 6, need be isolated and purified, combine to make this scheme nevertheless efficient We anticipate that the large amount of elimination which accompanies the [3 3]-sigmatropic rearrangement of trichloroacetimidate 5 may be suppressed in imidates bearing less electron withdrawing acyl substituents

SCHEME I



Acknowledgment We gratefully acknowledge financial assistance from the National Science Foundation under Grant No GP-38634X.

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2 Cf H. Kuehnis, R. Denss, and C J Eugster, Swiss Pattent 417, 591 (1968); Chem Abstr., 68, 39482 n (1968).

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4 L E Overman, J. Amer Chem Soc , 96, 597 (1974)

5 A. van der Gen, K. Wiedhaup, J J. Swoboda, H. C Dunathan, and W. S Johnson, ibid , 95, 2656 (1973).

6 All new compounds showed ir and pmr spectra consistent with the indicated structures and correct combustion analyses, except imidate 5 which was characterized by spectral properties alone

7 K. J. Clark, G I Fray, R. H. Jaeger, and R. Robinson, Tetrahedron, 6, 217 (1959)

8 Catalytic hydrogenation afforded 1-azaspiro[5 5]undecan-2-one, which was identical with an authentic sample[3] kindly provided by Professor R K Hill