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INTRAMOLECULAR [4+2] CYCLOADDITION REACTIONS OF ENAMINES AND ENAMIDES

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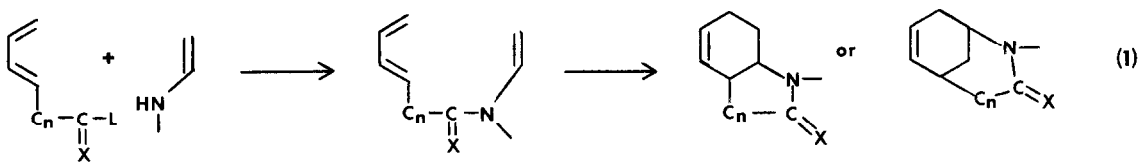
An attempt to utilize a new strategy for alkaloid synthesis which features the intramolecular [4+2] cycloaddition of enamines and enamides for the construction of the tetracyclic spiroamine skeleton characteristic of the *Erythrina* alkaloids was unsuccessful, unexpectedly giving a bridged cycloadduct rather than a fused one.

The hydroindole and hydroquinoline ring systems are common to a diverse array of alkaloid natural products. In order to develop a general strategy for the synthesis of alkaloids possessing these synthons, we initiated a program to evaluate the feasibility of employing the intramolecular [4+2] cycloaddition reactions[1] of nitrogen substituted dienophiles and dienes for the construction of functionalized hydroindoles and hydroquinolines. Since several examples of the intramolecular[2] cycloaddition reactions of dienamides were known at the outset of this investigation, our initial efforts were focused upon an examination of the heretofore unknown intramolecular cycloaddition reactions of enamines and enamides with *unactivated* dienes[3,4] utilizing the general approach depicted in eq. 1.



(1)

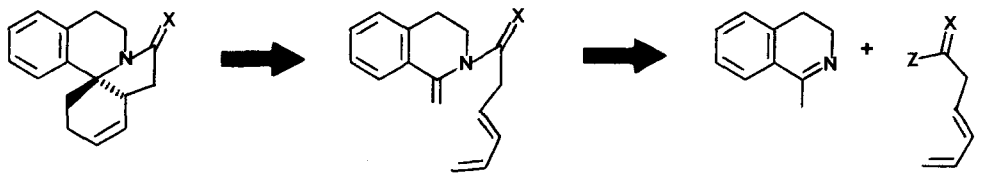
1 2 3 4 5

X = H_2 or O
n = 1,2

There are several features of this attractive strategy for the construction of nitrogen heterocycles which merit brief discussion. For example, the stage for the crucial intramolecular [4+2] cycloaddition reaction may be set with remarkable ease by the facile coupling of an electrophilic site on the diene moiety 1 with the nitrogen of an imine or enamine 2. Moreover, the highly favorable entropic assistance inherent in intramolecular reactions[1] augurs well for a successful cycloaddition between an electron rich diene and an electron rich dienophile, despite their noncomplementary donor-acceptor properties. The regiochemical and stereochemical outcome of intramolecular cycloaddition reactions will depend upon the

relevant double bond geometries together with the subtle differences in the transition state energies for each of the possible relative orientations of the diene and the dienophile. Although the preferential formation of the fused cycloadducts 4 might be expected based upon the reported intramolecular cycloadditions in systems geometrically related to 3,[1] a prediction of the stereochemistry of the ring fusion of the new hydroindole 4 (n=1) or the hydroquinoline 4 (n=2) is more difficult.

In order to assess the viability of this new strategy for alkaloid synthesis, efforts were initially directed toward the construction of the tetracyclic, spiroamine skeleton 6a, b characteristic of the *Erythrina* alkaloids employing the retrosynthetic format illustrated in eq. 2. Unfortunately the direct coupling of the triflate 9a (Z=OTfl) or the acid chloride



(2)

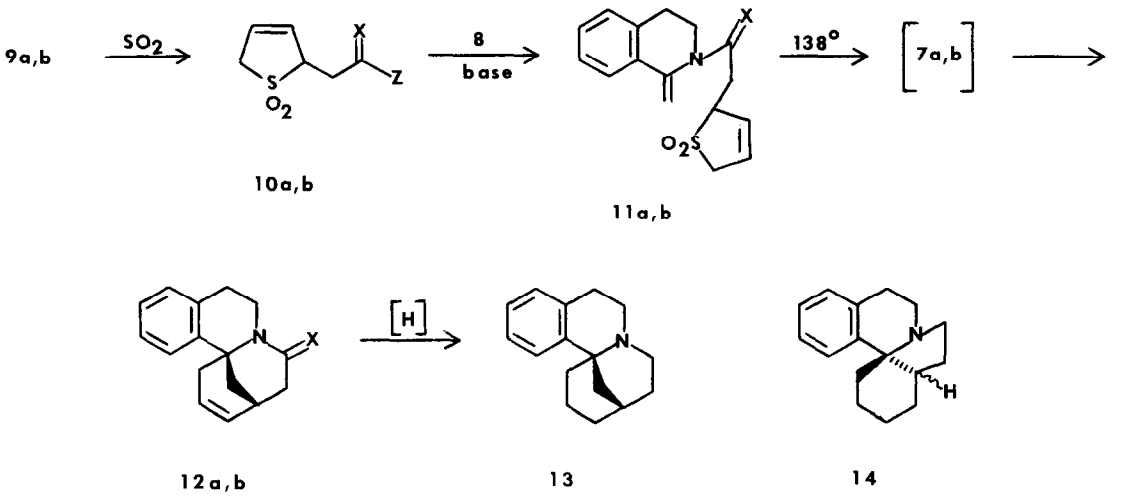
6a,b 7a,b 8 9a,b

Series a: $X=H_2$
Series b: X=O

9b (Z=Cl) with 1-methyl-3, 4-dihydroisoquinoline (8) gave the enamino diene 7a and the enamido diene 7b in abysmal yield. However, this crucial carbon-nitrogen bond forming step was easily effected by the highly useful expedient of masking the diene moiety as a 2-substituted-2, 5-dihydrothiophene-1, 1-dioxide (Scheme 1). Thus, reaction of the alcohol 9a (Z=OH)[5] with sulfur dioxide at room temperature in the presence of dihydroquinone produced the alcohol 10a (Z=OH)[6] (85%). Subsequent treatment of 10a (Z=OH) with triflic anhydride in methylene chloride in the presence of anhydrous potassium carbonate afforded the triflate 10a (Z=OTfl) which was not isolated but allowed to react *in situ* with the dihydroisoquinoline 8 to give the masked enamino diene 11a. The subsequent thermolysis of 11a in refluxing xylene (24h) led to the rapid evolution of sulfur dioxide and the slow formation of a cycloadduct in 36% overall yield. While the cycloadduct was initially believed to be 6a, catalytic hydrogenation (PtO_2/H_2/HOAc) produced a dihydro compound (98%) which was not identical with either of the known tetracyclic spiroamines 14.[7] An X-ray analysis of the hydrobromide salt (mp 238°C dec) of this dihydro cycloadduct unequivocally established the structure as the unexpected bridged compound 13.[8] The product of the intramolecular cycloaddition reaction therefore was probably 12a.

Hoping that an intramolecular cycloaddition of a less electron rich dienophile with an unactivated butadiene would proceed with the desired regioselectivity, the thermolysis of the enamide 11b was also examined. Thus, reaction of the acid 9b (Z=OH)[9] with sulfur dioxide in the presence of hydroquinone at 40°C afforded the carboxylic acid 10b (Z=OH)

SCHEME 1



Series a: X=H_2
Series b: X=O

(74%; mp 116-117°C). The acid 10b (Z=OH) was treated with thionyl chloride in benzene and the resulting acid chloride 10b (Z=Cl) (99%; mp 52-53°C) was then allowed to react with the dihydroisoquinoline 8 in the presence of triethylamine to give the enamide 11b [65% overall; mp 132-133°C; NMR ($CDCl_3$) δ 7.50-7.75 (m, 1H), 7.08-7.35 (complex, 3H), 6.00 (s, 2H), 5.82 (d, 1H, J=1 Hz), 5.17 (d, 1H, J=1 Hz); IR ($CHCl_3$) 1634 cm^{-1}]. Upon thermolysis of 11b in refluxing xylene (20h), sulfur dioxide was rapidly evolved to give the enamido diene 7b which underwent a facile intramolecular [4+2] cycloaddition to give the bridged cycloadduct 12b [97% overall; mp 95-96°C; NMR ($CDCl_3$) δ 5.58-6.00 (m, 2H), 4.76-5.05 (m, 1H); IR ($CHCl_3$) 1615 cm^{-1}]. This structural assignment was readily confirmed by reduction of the lactam 12b using lithium aluminum hydride to give a compound (91%) which was spectroscopically identical (^1H NMR, ^{13}C NMR, IR, MS) with the amine 12a obtained previously.

The unexpected formation of the bridged cycloadducts 12a, b rather than the fused bicyclic adducts 6a, b merits brief discussion. Although it has not been possible to unequivocally establish the stereochemistry of the intermediate enamino and enamido dienes 7a and 7b, respectively, the formation of *trans* double bond at $C_{3,4}$ is not only precedented,[10] but it is also supported by the fact that the thermolysis of 10a (Z=OH) in refluxing xylene produced *E*-3, 5-hexadien-1-ol (9a, Z=OH) with a high degree (>90-95%) of stereoselectivity. Since *trans→cis* isomerization under the reaction conditions does not seem likely, it would, therefore, appear that the *trans*-enamino diene 7a and the *trans*-enamido diene 7b undergo the cycloaddition reaction. An inspection of molecular models strongly suggests that the transition state for a "concerted," intramolecular [4+2] cycloaddition of 7a and 7b to give the bridged cycloadducts 12a and 12b, respectively, is highly strained, and a stepwise reaction

therefore seems plausible.[11] Although the formation of 7a and 7b might still be predicted based upon the stability of the various possible diradical intermediates, steric and/or conformational factors seem to kinetically favor the production of the diradicals which undergo cyclization to give 12a and 12b. However, the possibility that 12a and 12b are formed as the products of thermodynamic control via intermediate vinyl cyclobutanes or even 6a,b cannot be rigorously excluded at the present time. Studies to further elucidate the mechanistic course of these cycloaddition reactions are in progress.

Even though the desired erythrinane skeleton was not produced in these intramolecular [4+2] cycloaddition reactions, these observations remain highly significant. They are among the first examples of cycloadditions between the electron-rich dienophiles enamines and enamides with unac tivated butadienes. Other examples of related cycloaddition reactions which do proceed predictably to form alkaloid ring systems are under active investigation and will be reported independently.

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