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Synthesis of novel heterocycles based on the structures of erythrina alkaloids

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Abstract—Erythrina alkaloids represented by structure (**1**) are known to possess potent CNS activities. In this article, we have completed the synthesis of modified heterocyclic core structures (**4**) of erythrina alkaloids incorporating groups, which are expected to be metabolically more stable. Finally, we have oxidatively rearranged (**4**) to yield novel heterocycles (**5**).

1. Introduction

One of the most challenging problems for a medicinal chemist is to identify a structural lead for the discovery of drugs. There are essentially three sources for this which involve (a) screening of natural products, (b) screening of corporate library of compounds, and (c) structure based drug design. Ideally the alternative (c) will be most preferred, however, the structures of receptors are usually not available by X-ray analysis and the structures of target enzymes are not routinely available in most laboratories. It should be noted[1] however that several novel enzyme inhibitors have been discovered based on the X-ray structural studies. In recent years natural product research has been de-emphasized in most pharmaceutical companies for a variety of reasons including the logistic of collection of materials, etc. Combinatorial chemistry in the mean time has become the main stay in the industry and using this technology large number of compounds are being synthesized and added to the corporate library of compounds. These libraries are becoming the major sources of initial leads in drug discovery. Majority of these compounds are heterocycles and the compound collections are based on analogs of active leads discovered over a period of years. The importance of enriching these libraries by the addition of newer heterocycles cannot therefore be over emphasized.

Although many natural products[2] are already in use in human medicine and have been for many centuries, there are others, which have not found use because either they are toxic or they get metabolized[3] by P450 enzymes when administered to animals or humans. Many brilliant synthesis[4] of natural products have been achieved in the past and continues to attract the interest of chemists around the world. These efforts have not only enriched organic chemistry but also provided ways of modifying or making analogs of natural products for drug discovery.

2. Present study

However we wondered whether there could be an alternative approach involving synthesizing modified version of natural products of interest in which drug like features have been incorporated. Perhaps these modified natural products could then be rearranged to make novel heterocycles. In this letter we would like to highlight one such idea.

Erythrina alkaloids[5] such as erysotrine (**1**), erysotamidine (**2**), and ermelanthine (**3**) show potent CNS activities and represent challenging synthetic targets. Indeed several synthesis[6] of this group of alkaloids have been reported. These alkaloids possess several sites, which could be metabolized by P450 enzymes. We therefore decided to replace some of these metabolically vulnerable sites with groups, which are found in drugs and known to be metabolically stable. In our design we also decided to incorporate the ease of synthesis as an

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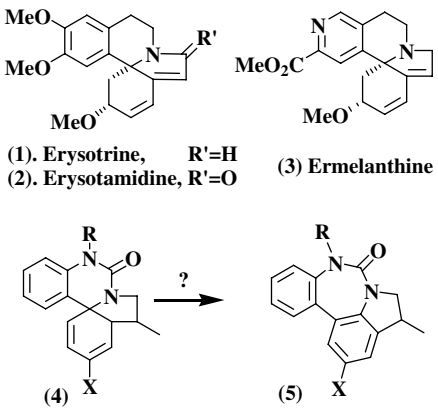


Scheme 1.

important criteria. Thus we wanted to synthesize compounds represented by structures (**4**), which we hoped to oxidatively rearrange to novel heterocycle (**5**). In short, the structures (**4**) and (**5**) are both derived from ideas presented by nature and yet they are unlikely to be natural products (see Scheme 1).

In this letter we wish to disclose a convenient synthesis of (**4**) and also its oxidative rearrangement to (**5**). We do realize that in structure (**4**) the conjugated diene system is not completely devoid of metabolic degradation, however, we only view it as the starting point for the synthesis of novel heterocycles including (**5**). Our synthetic schemes would allow several modifications in the structures of (**4**) and (**5**) and thus a library of compounds could be prepared for screening.

In a recent publication[7] we have reported that when the diallyl urea (**6**) is treated with tributyl tin hydride (TBTH) it yielded compounds (**7**)–(**11**). The major product in this reaction, not unexpectedly, was (**7**) formed by the addition of the initial phenyl radical to the *N*-allyl function. The formation[7] of (**8**)–(**11**) could be explained through the intermediacy of radical (**12**) (see Scheme 2).

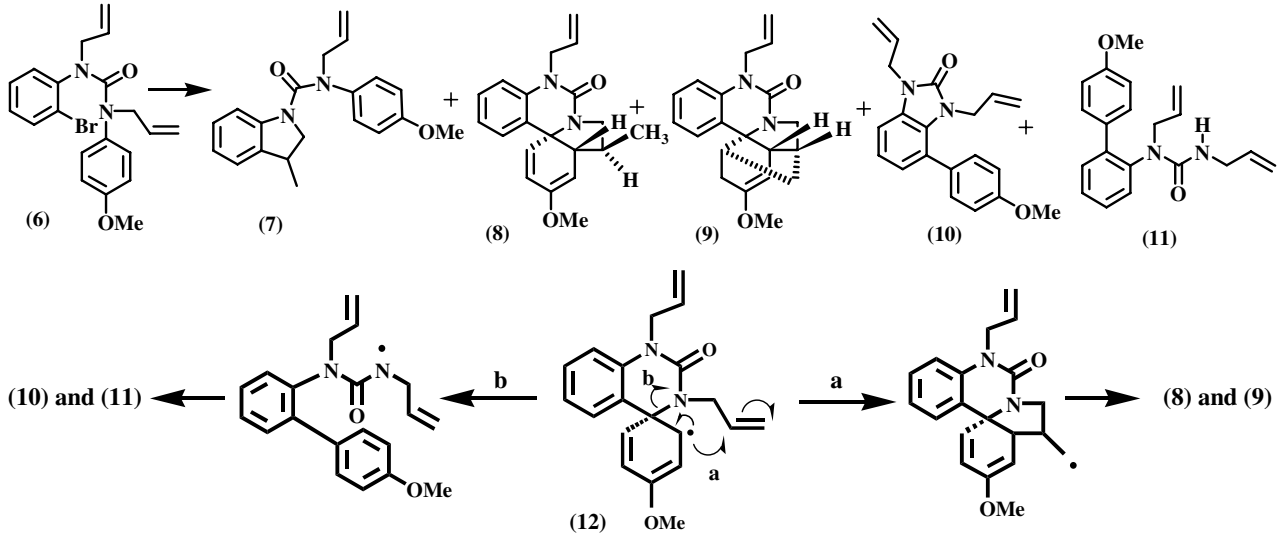
As we were interested to synthesize compounds of the type (**8**) and (**9**) and study their oxidative rearrangements we repeated these experiments with mono *N*-allyl ureas (**13**–**16**). This will avoid the formation of compounds such as (**7**) and the absence of the second allyl group will circumvent any problem in the choice of reagents required for the oxidative rearrangements.

Thus compounds[8,9] (**13**)–(**16**) were conveniently prepared[8] by the treatment of *N*-methyl bromo aniline with various substituted phenyl isocyanates in the presence of 10% equivalent of magnesium bromide. It should be noted that without the addition of magnesium bromide the formation of ureas proceeded extremely slowly and in poor yields. N-Allylation of these ureas yielded (**17**)–(**20**). The results of the reactions of (**17**)–(**20**) with TBTH are summarized in Scheme 3.

We planned to achieve the desired oxidative rearrangement using *N*-bromo succinimide. We expected allylic bromination to occur first and the resulting compound will then undergo spontaneous rearrangement with concomitant loss of hydrogen bromide to yield the novel heterocycles (**5**) (see Scheme 4).

In the event when we treated (**22**) and (**23**) in dichloro methane solution with 2 equiv of NBS they were smoothly converted in excellent yield to (**39**) and (**40**), respectively. Debromination of (**39**) with TBTH yielded (**41**) (Scheme 5). We are in the process of studying Heck and Suzuki reaction with (**39**) and (**40**).

To understand at which stage the bromination of the aromatic ring occurred, we treated (**23**) with 1 equiv of NBS and obtained (**42**). Treatment of (**42**) with a second equivalent of NBS yielded (**40**) thus establishing that bromination of the vinyl ether precedes allylic bromination. It is interesting to note that when (**22**) was treated in chloroform (which contains a small amount of ethanol) solution with NBS it yielded a crystalline



Scheme 2.